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Pathology of Oral Mucosa
(Lectures for the 5th year students)
Part I

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Normal oral mucosa

In its basic structure the oral mucous membrane resembles other lining mucous membranes, for example, those of the vagina or the oesophagus. Within the mouth, however, there is a wider range of epithelial thickness than that seen at other mucosal sites. These variations depend largely on differences in the degree of keratinization shown by the mucosae in different areas of the mouth. Some of the reactions of the oral mucous membrane resemble those of the skin, presumably because of its position in the transition area between the gastrointestinal tract and the skin. As a result of this, diseases of both mucous membranes and skin may produce lesions in the mouth. Its behaviour in disease processes perhaps most closely resembles that of the vaginal mucosa.

The epithelium covering the oral mucosa shows a wider variation in thickness and in its pattern of keratinization than mucous membranes at other sites.

The oral mucous membrane consists both anatomically and functionally of two layers: one (the corium or lamina propria) essentially of mesodermal origin and one epithelial. When considering variations of structure, the behaviour of the corium must be taken into account even though the major changes may appear to be within the epithelial layer.

The keratinocytes are the main cell component of the oral epithelium but other cell types include melanocytes, Langerhans cells, and Merkel cells.

In normal mucous membrane the integrity of the epithelium is maintained by the division of keratinocytes in the basal layer. As each cell divides one resulting cell remains effectively in situ, while one migrates towards the surface, undergoing various structural modifications as it passes through the epithelium. These modifications, which are dependent on the process of keratinization, vary according to the precise site of the mucosa involved and result in the production of a surface layer of cells that are either fully, partially, or non-keratinized and which are shed into the oral cavity at a rate dependent on the rate of mitosis in the basal layer. For each dividing cell, one cell is lost from the surface and, thus, the integrity and dimensions of the epithelial layer are maintained. The rate of turnover of these cells, that is, for a keratinocyte in the basal layer to reach the surface in various human epithelia has been determined by a number of techniques. The rate in human skin is generally quoted as being of the order of 50 to 70 days and that in the gingival epithelium much the same, but that in the buccal epithelium is much faster of the order of 25 days.

The epithelium of the oral mucosa shows wide variations in the extent of the keratinization process. In the fully keratinized situation, the rather cubical cells formed by mitosis at or near the basal layer migrate towards the surface, becoming more polyhedral and sharing intercellular attachments, which have given the name prickle cell layer (or stratum spinosum) to this zone. In the light microscope these intercellular prickles appear as single attachments of the cell walls, but by electron microscopy these intercellular junctions (referred to as desmosomes) are seen to be of much greater complexity. It is probable that the desmosomes act in a mechanical manner to give strength to the epithelium. In several diseases marked by epithelial fragility the desmosome attachments are lost or impaired. It should perhaps be added that similar, one-sided structures, hemidesmosomes, attach the plasma membrane of the basal keratinocytes to the lamina lucida of the basement membrane complex. As the cells of the stratum spinosum migrate to the surface they begin to flatten and granular structures (keratohyalin granules) appear within them. These granules give the characteristic appearance to the stratum granulosum in keratinized epithelia. Finally, at or near the surface, the epithelial cells lose their detailed inner structure, the nuclei degenerate, the keratohyalin granules fragment and disappear, and the insoluble protein complexes mentioned above fill the cell, now fully keratinized. At this stage the desmosomes have effectively degenerated also and the flattened cells are eventually lost into the oral cavity. As has been pointed out, each

keratinized cell lost in this way must be matched by a dividing cell in the proliferating compartment of the epithelium in order for stability to be maintained. This process of renewal applies only to fully keratinized epithelium as seen, for instance, in the mucous membrane overlying the hard palate and is usually referred to as orthokeratinization. In other areas (as in some parts of the buccal mucosa and the floor of the mouth), this process of keratinization does not take place, keratohyalin granules are not formed, and nuclei and organelles (although somewhat effete) can be seen in the surface layers. In an intermediate form (parakeratotic epithelium), nuclei may still be seen in the surface layers and keratohyalin is sparse or absent. For the purpose of understanding the clinical significance of these differences in keratinization, they should be regarded as being part of a spectrum ranging from complete non-keratinization at one extreme, through varying degrees of parakeratinization, to full orthokeratinization at the other.

The distribution of these differing epithelia in the normal oral mucosa has a close relationship with the function of the tissues at the site. In normal mucosa, non-keratinized or parakeratinized epithelium is seen on the buccal mucosa, the floor of the mouth, and the ventral surface of the tongue, whereas orthokeratinized epithelium is seen on the hard palate and parts of the gingivae. The dorsal surface of the tongue is also orthokeratinized, but differs from the other oral mucosal surfaces in that there are a number of specialized structures present, predominantly the papillae. There are four types of lingual papillae: anteriorly the filiform and fungiform; posteriorly foliate and vallate papillae. The filiform and fungiform papillae are of clinical significance in that their atrophy is often an early sign of mucosal abnormality.

Lingual tonsil, foliate papillitis

Lingual tonsil tissue is mainly located on the posterior part of the lateral aspect of the tongue and may be associated with vertical folds of mucosa, sometimes referred to as foliate papillae. Small aggregates of subepithelial lymphoid tissue are occasionally found elsewhere in the oral cavity. Diseases of lingual tonsillar tissue are uncommon, but they may become enlarged as a result of trauma from teeth or dentures, inflammation, or reactive hyperplasia of the lymphoid tissue. Inflammatory changes are sometimes referred to as foliate papillitis. Occasionally, crypts may become obstructed and undergo cystic dilatation as a result of accumulation of squamous debris.

There is currently a great deal of research concerning genetic abnormalities of keratinization, particularly disturbances in the genes coding for specific keratins that are responsible for diseases, such as epidermolysis bullosa. In addition, cell adhesion and the molecules associated with it (for example, cadherins and integrins) are of great importance in disorders of the skin and mucous membranes. In the pemphigus group of immune-bullous diseases, there is faulty adhesion between keratinocytes due to the development of auto-antibodies against desmoglein I and III, which are members of the cadherin family of adhesion molecules.

The melanocytes appear in, or very close to, the basal layer and on electron microscopy show granular structures (melanosomes) that are the precursors of melanin the black pigment that modifies the colour of both skin and mucous membranes. These cells, like the Langherhans cells, are dendritic with cytoplasmic prolongations extending between the cells of basal and suprabasal areas of the keratinocytes. Melanocytes synthesize but do not retain melanin; it is transferred by the dendritic processes to adjacent keratinocytes. The melanotic pigmentation of oral mucosa, like that of the skin, shows great racial variation. However, this does not depend on variation of the numbers of melanocytes but on the number and activity of the melanosomes within them. The epithelia of all races contain approximately the same number of melanocytes. It is the rate of production of melanin and its distribution that are different. It is known that hormonal influences are important in the stimulation of melanocyte activity, although the precise mechanisms remain obscure. In some circumstances the melanocytes may be stimulated to produce excess melanin by a wide range of non-hormonal stimulae.

The Langerhans cells were first identified in 1860, and for a long time were something of a mystery. There is a substantial number of these cells present near the basal complex of the oral epithelium, with dendritic processes extending between the keratinocytes and with recognizable ultrastructural features. Over the last 3-4 decades research has shown that these cells have an

immunological function, acting as peripheral scavenging cells of the immune system, rather like macrophages but lacking their ability to phagocytose effectively. It would seem that at least one function of these cells is to act as antigen-presenting cells and stimulate the activation of T lymphocytes against them. Langerhans cells are therefore considered to be immunologically competent dendritic cells, similar to those found in the peripheral lymphatic system. Their origin appears to be the bone marrow and not the epithelium.
Keratinocytes and Langerhans cells play an important part in the immune-surveillance of the oral epithelium, and both secrete and respond to immunologically active cytokines, including the interleukins and interferons. The concept of localized mucosal immunity is currently under investigation with regard to both its function in maintaining the integrity of normal tissue and its role in mucosal disease. The pathogenesis of lichen planus is not yet fully understood, but probably involves a cell-mediated immune response to an external agent, in which Langerhans cells and keratinocytes release cytokines and adhesion molecules to which T lymphocytes can bind. Subsequent activation of cytoxic lymphocytes is thought to be responsible for damage to the basal cells, which is a characteristic feature of this condition.
So Langerhans cells are immunologically competent dentritic cells.
The corium (lamina propria) of the oral mucous membrane is separated from the submucosal layer, by a zone of gradual transition rather than a clear boundary. In the corium and submucosa lie the minor salivary glands and sebaceous glands of the oral cavity. These are widely variable in distribution, the mucous glands being most frequent in the mucosa of the lips and posterior palate, whilst the sebaceous glands are mostly concentrated in the buccal mucosa where they may appear as yellow spots, known as Fordyce's spots. Fordyce's spots are the sebaceous glands of the oral mucosa. They are frequently mistaken for pathological lesions but are completely normal.

FORDYCE'S GRANULES

Fordyce's granules are ectopic sebaceous glands (normal tissue in an abnormal location) within the oral mucosa. Normally, sebaceous glands are seen within the dermal adnexa, in association with hair follicles; however, Fordyce's granules do not exhibit any association with hair structures in the oral cavity. This condition is seen in approximately 80 to 90% of the population.
Fordyce's granules present as multiple yellowish white or white papules. They are often seen in aggregates or in confluent collections, most commonly on the buccal mucosa and vermilion border of the upper lip.
Occasionally, these may be seen on the retromolar pad area and the anterior tonsillar pillars. Men usually exhibit more Fordyce's granules than women exhibit. The granules tend to appear during puberty and increase in number with age.
Fordyce's granules are completely asymptomatic and are often discovered on routine examination. Histologically, they are identical to normal sebaceous glands found in the dermis.
Usually no treatment is indicated, and since the clinical appearance is virtually diagnostic, no biopsy is usually required. Fordyce's granules on the vermilion border of the upper lip may require surgical removal for esthetic reasons.
Rare cases of pseudocysts and sebaceous cell hyperplasia and adenoma have been reported.

The submucosal tissue components are also widely variable: blood vessels, fat, and fibrous tissue being present in differing proportions according to the precise site. Within the corium and submucous tissues are scattered cells of the leukocyte series in varying proportions and concentrations. During disease processes these may alter radically, both in number and in type, depending on the basic nature of the pathological process involved.

The basement membrane

Lying between the epithelium and corium of the oral mucous membrane is a complex multilayered structure, the basement membrane. On ultrastructural study it is seen that the components of the basal zone are much finer than suggested by light microscopy and that, rather than a single membrane, a number of layers are visible, including the lamina lucida and the lamina densa. In the basement membrane, anchoring fibres attach the lamina densa to the underlying tissue and hemidesmosomes attach the basal cells of the epithelium to the lamina lucida. Below the level of

the hemidesmosomes is the subbasal dense plate, through which anchoring filaments connect the lamina lucida to the lamina densa. Autoantibodies to components of the lamina lucida have been identified in bullous pemphigoid, which is an immunobullous skin disease.

Although the oral mucous membrane has several functions, sensory and secretory among them, its main purpose is probably that of acting as a barrier. It protects the deeper structures from mechanical insults, such as masticatory trauma and also prevents the entry of micro-organisms and some toxic substances. The oral mucosa has an extensive sensory innervation that can discriminate touch and temperature. Taste buds are also located in oral epithelium. In considering the protective function of the oral mucosa, it is also necessary to discuss other factors, in particular the role of saliva. The oral mucosa is constantly bathed by saliva, which not only maintains the physiological environment necessary for the maintenance of epithelial integrity but also includes several protective, antibacterial components. A number of these have been described, but perhaps the most important are the secretory immunoglobulins, predominantly of the IgA class, that are found in saliva and that attach to sites on the epithelial surface. In spite of this barrier function of the oral mucosa, there is a degree of permeability that, apart from its theoretical and scientific interest, is also of clinical significance. During local therapy with mouthwashes and similar preparations, drugs may be transported across the oral mucosa and may exert effects similar to those resulting from systemic therapy. This is an important factor when considering the use of high-concentration steroid mouthwashes for ulcerative lesions of the oral mucosa. The permeability of the oral mucosa is utilized in the treatment of angina by glyceryl trinitrate. In these circumstances rapid absorption of the drug throughout the oral mucosa is an obvious advantage.

Although the full significance of the role of saliva in maintaining the health of the oral mucosa is, as yet, not fully understood, there can be no doubt that a free salivary flow is an essential part of the oral environment. If the flow is diminished, either by degenerative changes in the salivary glands or by the action of drugs, soreness and atrophic changes in some areas of the oral mucosa rapidly follow. The tongue is perhaps most markedly affected in this way. In some conditions, it is difficult to distinguish between primary mucosal changes and those secondary to diminished salivary flow, but on a clinical basis it is reasonable to accept that atrophic changes in the oral epithelium are regularly associated with dryness of the mouth. The main immunologically active component of saliva is IgA, which is present in a much higher ratio to other immunoglobins, than in the serum.

A further component to be considered as part of the normal healthy oral environment is the microbial flora of the mouth. A wide range of micro-organisms may be present in the oral cavity, living in a commensal relationship with the host. When this relationship is upset by a change in the local or generalized conditions, the commensal micro-organisms may become pathogenic. Oral candidosis is an example of this, although the precise change in the host leading to clinical infection is not easy to identify.

Changes occur in the oral mucosa of healthy individuals with increasing age. Reductions in overall epithelial thickness, flexibility of the collagen fibres, innervation, blood supply, and permeability of the mucosa have been described. It has generally been assumed that changes of this kind occur with comparative suddenness at a late age, but recent evidence implies that, at least in the case of the epithelium of the tongue, a continuous trend towards atrophy occurs throughout adult life. The clinical significance of this observation is that sudden changes in the structure of the oral mucosa, such as depapillation of the tongue, should never be considered as being due to age alone without full investigation and the elimination of other factors such as haematological and nutritional disorders.

Age changes in the oral mucosa

Although a variety of changes may occur in the oral mucosa of the elderly, distinguishing those attributable to ageing from those due to systemic disease, nutritional deficiencies, or the side-effects of medication can be difficult. Atrophic changes have been reported in lingual mucosa related to an almost linear reduction in epithelial thickness with increasing age, by about 30 per cent of the initial thickness around 85 years of age. However, this may not apply to other oral mucosal surfaces. The question of whether increased keratinization of the oral mucosa occurs in old age has not been resolved.

Oral mucosal connective tissues become more fibrosed, less vascular, and less cellular with age. Atherosclerotic changes are also seen in arteries of the oral mucosa, and a progressive, partial ischaemia may contribute to some of the atrophic changes.
Certain local oral mucosal lesions are reported to occur more frequently in the elderly, examples being sublingual varicose veins, increased prominence of Fordyce's granules, and enlargement of foliate papillae, but supportive evidence is often lacking.
Age changes may also affect the function of salivary glands. It has been shown that gradually increasing degrees of atrophy and fibrosis affect the secretory units of both the submandibular and the labial salivary glands throughout life, even in the absence of disease processes that might be associated with such change.

Abnormal oral mucosa

Many oral lesions represent the end result of breakdown or abnormality of the normal structuring of the epithelium. Variation in the rate of keratin formation, disproportion between the different layers of the cells, breakdown of the normal intercellular bonds of the prickle cells, splitting of the epithelium from the connective tissue, and many other similar abnormalities may occur in different diseases. For instance, in a number of mucosal abnormalities hyperkeratosis occurs. This may arise as a result of abnormal irritation of the mucosa or apparently spontaneously in some conditions. In other lesions, atrophy of the epithelium may occur. This represents a thinning of the normal epithelial layer, perhaps to only a few layers of cells, often accompanied by incomplete keratinization. Such epithelium is easily lost following a minor degree of trauma and thus atrophic lesions of the mucosa readily become ulcerated. Many of the so-called erosive lesions are of this type. It should be remembered that ulceration is in itself a quite unspecific process and implies only the loss of epithelium from the mucosal surface followed by inflammatory changes in exposed connective tissue. Bullae or blisters of the mucosa may occur in one of two ways, either by degeneration of the cells and of the intercellular links in the prickle cell layer of the epithelium or by separation of the whole of the epithelium from the underlying corium. Frequently, there are also changes in the supporting tissues and, in some cases, the visible epithelial changes may be secondary to changes in the underlying corium that affect the nutrition and metabolism of the epithelium. The greatest practical significance of this fact is, perhaps, the necessity, when taking a biopsy of lesions of the oral mucosa, to include a representative thickness of corium in the tissue removed for microscopic examination. In many cases, a biopsy consisting largely of epithelium alone is virtually useless for diagnosis.
The integrity of the oral mucosa is maintained by a complex of interacting factors superimposed on the localized stabilizing mechanisms discussed above. The general hormonal status of the patient and a number of nutritional and metabolic factors are involved in maintaining the cell metabolism and the ordered structure of the mucous membranes. The role of iron metabolism in the maintenance of the structure of the oral mucosa has been the subject of much investigation. It is certainly the case that iron deficiency, even when relatively mild in clinical terms, can result in generalized oral epithelial atrophy and loss of the papillary pattern of the lingual mucosa. It seems that other deficiencies that might affect iron metabolism and erythrocyte production, such as folate and vitamin B_{12} deficiencies, may also contribute to this destabilization of the oral epithelium. If any single factor is disturbed, then sequential changes occur and clinically significant abnormalities of the oral mucosa may follow. It is often difficult to decide which of the various possible factors are involved in initiating these changes these may evidently occur either as a primary manifestation of localized mucosal abnormality or as a secondary effect of generalized disease processes. It is the role of oral physicians to assess the possible aetiological factors associated with mucosal lesions of this kind and to ensure appropriate investigations and (if needs be) management.
The reactions of the oral mucosa are not exclusively those of a mucous membrane. As has been pointed out, a number of diseases of the skin also find expression in oral lesions. This is not entirely surprising on anatomical grounds since the larger part of the oral mucosa is derived from an embryonic invagination that carries inwards some of the precursor epithelial cells from which both facial skin and oral mucosa are developed. As might be expected, the lesions of oral mucosa and skin that occur in these mucocutaneous diseases are often superficially different, although the basic

histological changes seen in the tissues are similar. Such differences are seen in the primary lesions and, presumably, depend on the differences between the structure of the mouth and that of the skin. Quite often secondary changes also occur in oral lesions. The continually damp environment of the mouth, in combination with repeated mild trauma of the tissues by teeth and foodstuffs, and the presence of a wide range of microbial flora further modify the nature of the lesions produced in a number of diseases. For instance, should the epithelium be thinned by atrophy or weakened by the formation of blisters, it is likely to be lost and the initial lesion be replaced by an ulcer. For reasons such as these, oral lesions, particularly at an advanced stage, may show features less characteristic than those of the equivalent skin lesions of the same disease. Clinical diagnosis in such circumstances may be quite difficult since only areas of ulceration of a relatively non-specific nature may be present rather than fully developed specific lesions.

Histopathological changes

It may be helpful to recall some of the terms used to describe changes seen on histological study of the oral mucosa.

- Hyperkeratosis: an increase in the thickness of the keratin layer of the epithelium, or the presence of such a layer in a site where none would normally be expected. Hyperorthokeratosis is the term used to specify a thickened, completely keratinized layer, whereas in hyperparakeratosis there is incomplete keratinization with nuclei remaining in the surface cells.
- Acanthosis: an increase in thickness of the prickle cell layer of the epithelium. This may or may not be accompanied by hyperkeratosis.
- Atrophy: a decrease in the thickness of the epithelium.
- Oedema: the collection of fluid in or between the prickle cells, intra- or intercellular, the two forms often occurring simultaneously. Oedema may also occur between the epithelium and the corium in the region of the basal complex.
- Acantholysis: loss of the intercellular attachments in the prickle cell layer leading to separation of the cells. When associated with intercellular oedema this leads to the production of intra-epithelial bullae or blisters.
- Atypia: a term used to describe variations in the maturation of the epithelial cells that may be associated with malignancy or premalignant potential. Such features as abnormal mitoses and lack of normal structure of the epithelium are taken into account in the assessment of atypia.
- Petechiae are tiny, well-circumscribed macules that represent punctate hemorrhages in the dermis. Conditions in which petechiae may occur include gonococcemia, meningococcemia, amyloidosis, and various vasculitis. Petechiae disappear after the underlying disease process has ceased.
- Ecchymoses, or bruises, are large dermal hemorrhages that occur most often after blunt trauma but may be due to platelet dysfunction or amyloidosis. They are red to purple initially but in time exhibit red, yellow, and green colors as the extravasated blood is degraded.

The oral mucosa in generalized disease

Oral lesions may occur in a wide variety of generalized diseases. This fact is important, not only because of the need to treat the often painful oral lesions, but also in view of their significance in providing a diagnostic indicator. The mouth is readily available for inspection (and for biopsy) and oral lesions may appear early in some diseases. Thus, a number of important conditions may be first diagnosed following the proper evaluation of oral lesions. The relationship between generalized and oral disease is a very complex one, but it may be helpful to identify three types of such interrelationships

Interrelationships between generalized and oral disease

In one group of conditions the oral lesions are similar in aetiology and histology to those found elsewhere in the body, being modified only by the oral environment. Many of the oral lesions of skin diseases fall into this group as well as those in some gastrointestinal conditions.

A second group of oral lesions results from changes in the metabolism of the tissue under the influence of abnormalities of nutrition, endocrine, and other factors. These abnormalities themselves are the result of some distant pathological process. The oral lesions associated with malabsorption fall into this group.

In this group both oral and more generalized lesions result from a systemic (and different) abnormality. Sjgren's syndrome, a manifestation of a generalized autoimmune disease resulting in *salivary gland hypofunction*, is an example of such an association.

Classification of the oral general disease relationships is difficult and may result in oversimplification. It is evident that more than one form of association might occur in a single case. For instance, a patient with a disease of the lower gastrointestinal tract might well produce primary lesions of the disease on the oral mucosa, as well as secondary mucosal change consequent to malabsorption.

Saliva and the salivary glands

A number of conditions affecting the salivary glands are managed surgically. These include cysts and neoplasms arising in the glands and also conditions arising as a result of the presence of calculi or other obstructions in the glands or ducts. However, with the elimination of these two groups of important salivary gland diseases there are remains a number of conditions that should be considered within the scope of oral medicine. This chapter will consider sialadenitis, sialosis, necrotizing sialometaplasia, and disturbances in salivary flow rate. The clinician should be cognizant with the functions of saliva and the anatomy of the salivary glands. This information is helpful in understanding the nature of the investigations required to study salivary gland disease, their ensuing sequelae, and the therapies available.

Saliva is a glandular secretion that is essential for the maintenance of healthy orodental tissues. Saliva is a complex fluid and many of the functions of saliva have a protective role. The physical properties of saliva vary according to the different types of salivary glands, with parotid secretions having a serous (watery) consistency. The submandibular and sublingual glands secrete has more viscous saliva due to their higher glycoprotein content. A severe reduction in salivary flow rate can have devastating consequences on oral health and, subsequently, on the psychological and social well-being of the sufferer.

Functions of saliva

Function	**Description**
Lubricant	Coats and protects the mucosa against mechanical, thermal, and chemical irritation
Cleanses the teeth	Clears food from the oral cavity and oral mucosa
Ion reservoir	Facilitates remineralization of the teeth
Buffer	Neutralizes plaque pH after eating
Antimicrobial	Secretory immunoglobulins, enzymes, and other salivary proteins help regulate the oral flora
Pellicle formation	A protective layer of salivary protein that forms over enamel acts as a diffusion barrier
Digestion	Salivary amylase initiates the digestion of starch
Facilitates taste	Saliva is a solvent and therefore allows the interaction of foodstuff with taste buds
Water balance	Dehydration causes a reduction in salivary flow rate with an associated oral dryness; this should stimulate a need to increase fluid intake

- Saliva is important for the maintenance of oral health.
- A diminution of salivary flow can have a detrimental impact on the quality of life of a patient.

The composition of saliva is affected by a number of factors, including the type of salivary gland. The majority of amylase is produced by the parotid glands but the blood group substances are secreted mainly by the minor mucous glands. The unstimulated flow rate is more important than the stimulated flow rate for oral comfort. However, the stimulated flow rate is important to facilitate chewing and swallowing during mastication. The submandibular gland contributes approximately 65 per cent of the resting whole salivary flow rate, only 15-20 per cent is derived from the parotid, with the sublingual and minor glands both delivering 7-8 per cent. In contrast, the parotid provides 45-50 per cent of the stimulated whole salivary flow rate. Salivary flow rates exhibit diurnal variation with an average unstimulated flow rate throughout the day of approximately 0.3 ml/minute in sleep this may fall to 0.1 ml/minute. Many textbooks mention that approximately 1500 ml of saliva is produced each day. More recently, however, it has been suggested that this figure is an overestimation of total daily salivary flow rate, and a daily flow rate of 500-600 ml/day may be a more realistic estimate.
The parotid glands are the largest salivary glands. They are wedge-shaped and situated in front of the ear and behind the ramus of the mandible. The apex of the wedge is the deepest part of the gland. The peripheral branches of the facial nerve (CN VII) are intimately associated with the parotid gland. This relationship is inadvertently demonstrated when an inferior dental nerve anaesthetic block is administered incorrectly, and causes a temporary drooping of the upper eye lid.
Parotid saliva is transferred along the parotid duct into the oral cavity. The thick-walled parotid duct (Stenson's duct) emerges at the anterior border of the parotid gland and runs over the surface of the masseter before hooking medially over the anterior muscle border. The orifice of the duct is covered by a small flap of mucosa called the parotid papilla and this is situated opposite the maxillary second permanent molar.
The two submandibular glands are approximately half the size of the parotids. The superficial part of the submandibular gland is wedged between the body of the mandible and the mylohyoid muscle, with the smaller deep part hooking around the posterior border of the muscle to lie on the floor of the mouth above the mylohyoid. The submandibular (Wharton's) duct runs forward, along the floor of the mouth to open into the subligual papilla, just lateral to the lingual frenum. The secretions are a mixture of serous and mucous fluids.
The sublingual glands are the smallest of the three pairs of salivary glands and are located just below the floor of the mouth beneath the sublingual folds of mucous membrane. There are numerous sublingual ducts that open into the mouth along the sublingual folds. The secretions of these glands are predominantly mucous.
The minor salivary glands consist of numerous small mucosal glands situated on the tongue, palate, buccal and labial mucosa. They produce primarily a mucous secretion.

Assessment and investigation of patients

Oral medicine is generally understood as being the study and non-surgical treatment of the diseases affecting the orofacial tissues, especially the oral mucous membrane, but also other associated tissues and structures such as the salivary glands, bone, and the facial tissues. Oral medicine is predominantly an out-patient speciality. The boundaries of oral medicine are poorly defined. For instance, the investigation of facial pain and other neurological disturbances may be considered to be in the field of oral medicine or of oral surgery. It is the responsibility of the general dental practitioner to diagnose and manage some of these conditions. Others are often better treated in specialist clinics, but the general dental practitioner, to a very great extent, bears the responsibility for the recognition of oral disease at an early stage.

Definition of oral medicine

Oral medicine is that area of special competence concerned with the health of and with diseases involving the oral and join-oral structures. It includes those principles of medicine that relate to the mouth, as well as research in biological, pathological, and clinical spheres. Oral medicine includes the diagnosis and medical management of diseases specific to the orofacial tissues and of oral manifestations of systemic diseases. It further includes the management of behavioural disorders and the oral and dental treatment of medically compromised patients.

The development of the discipline of oral medicine has depended largely on the adoption of an analytical approach based on the application of fundamental principles. It follows that the practice of oral medicine as a speciality depends largely on the availability of diagnostic facilities, often greater than those available to the general dental or medical practitioner. Perhaps the most important role of those working in the field of oral medicine is in the recognition of changes in the oral cavity resulting from generalized disease processes. Many oral lesions that, in the past, were considered to be of entirely local origin are now known to be associated with systemic abnormalities. For this reason specialists in oral medicine have a close working relationship with a large number of medical and surgical specialities. The most potent factor in the expansion of the scope of oral medicine was the change of emphasis from the purely descriptive to the investigative. The modern concept of the subject implies a recognition of basic aetiological factors, of the histopathological and molecular changes occurring in the involved tissues, and of the significance of such matters as the general medical status of patients. The challenge for the future of the speciality is to develop evidence-based management protocols.

History taking

The basis of any investigation is a careful and detailed clinical history and examination. The patient should be allowed to describe their complaint(s) and concerns in their own words. It is, however, often necessary to ask the patient for more precise or detailed information. The specific questions asked will depend upon the presenting complaint and this will be addressed in the appropriate chapters. Regardless of the orofacial condition that the patient has, it is important that the clinician, when questioning the patient, does not try to influence the patient's response. In addition, the patients must not feel as if they are being hurried. Sensitivity may be especially required for some conditions. As with all patient care, confidentiality is of the utmost importance.

It is of great importance to obtain details of the medical history of the patient and of any current or recent drug therapy. Similarly, the patient should be asked at this stage about their use of alcohol and tobacco. Some people are poor historians with regard to their medical history and it is therefore often necessary to ask the patient's general medical practitioner to fill in the details. This is particularly relevant when a patient has a chronic condition that has been managed by several specialists. The correspondence that the general medical practitioner has concerning such a patient can give great insight into the patient's complaint and care. In the hospital environment, the request for and careful reading through of the patient's general hospital case sheet can be, by far, the most productive method of assessment in complicated cases. When dealing with the past medical history it is necessary to use direct questioning on some points. As an example, soft-tissue lesions of the mouth may be associated with skin rashes, eye and genital lesions. The connection with mouth lesions may seem quite tenuous to the patient who may very well fail to volunteer information on these points unless directly asked.

The examination

When examining the mouth, the whole of the oral mucosa must be carefully examined. All removable appliances should be taken out. The practitioner should approach the examination of the patient in a systematic manner to ensure that all the relevant tissues have been seen. The lips and cheeks must be gently retracted to display the full extent of the sulci and the tongue gently held with the aid of a gauze napkin, and extended forward and to each side. Care must be taken that the whole of the floor of the mouth and undersurface of the tongue is seen. The posterior part of the tongue, tonsillar fauces, soft palate, and part of the pharynx are exposed by gentle pressure on the tongue and helped by phonation of by the patient. This examination of the oral mucosa must be combined with a careful assessment of the other dental structures, facial skeleton, salivary glands, and soft

tissues of the face and neck. A search for palpable lymph nodes should be made, remembering that normal lymph nodes are not detectable by simple palpation. Practitioners should be familiar with the tests required to assess gross function of the cranial nerves, in particular the fifth and seventh cranial nerves.

The extraoral examination may be extended to include the general appearance and demeanour of the patient. The eyes, scalp, neck, hands, and the skin of the face and arms should usually be inspected to obtain significant information. Each of these visually accessible areas can demonstrate signs that alert the practitioner to possible underlying systemic disease.

The intraoral examination should take place with an adequate light source. Sometimes tissues require drying to enable thorough visualization this is particularly relevant to teeth. Occasionally, in patients with a parchment dry oral mucosa, it is helpful to allow the patient to rinse with water before continuing with the intraoral examination this will help lubricate the soft tissues and prevent your gloves or mirror sticking to and traumatizing the tissues. Conversely, in some patients with copious viscous saliva, a mucolytic mouthwash may be helpful prior to intraoral examination.

Useful information from extraoral examination

Observation	**Information (examples of associated conditions)**
General demeanour, appearance, and manner	Wasted, undernourished, cachectic appearance, (e.g. malnutrition, eating disorder, underlying malignancy); low mood, anxiety, agitation (e.g. depression)
Breathlessness	Cardiorespiratory problems
Face	Shape and symmetry (masseteric hypertrophy, craniofacial syndromes); Cushingoid appearance (e.g. corticosteroid therapy); neurological deficits (e.g. Bell's palsy, cranial tumours); cyanosis (e.g. cardiorespiratory disease); pallor (e.g. anxious, unwell, anaemic)
Scalp and facial hair	Scant hair (e.g. ectodermal dysplasia)
Eyes	Conjunctival scarring (e.g. pemphigoid); pale sclera (anaemia); yellow sclera (jaundice); exophthalmia (hyperthyroidism); xanthomas of periocular skin (hypercholesterolaemia)
Neck	Enlarged lymph nodes (oral infection, neoplasms); goitre
Hands	Raynaud's phenomenon; koilonychia and other lesions of the nails; fingers: joint swelling and acquired disfigurement (rheumatoid arthritis); Hebden's nodules (osteoarthrosis); palmar keratosis (Papillon-Lefvre syndrome); liver palms; tobacco staining; finger clubbing (chronic cardiorespiratory problems, including infective endocarditis)
Wrists	Purple papules consistent with lichen planus
Skin	Petechiae or ecchymoses (e.g. blood dyscrasia); cyanosis (cardiac or pulmonary insufficiency); jaundice; pigmentation (possible endocrine problems)

Investigations

A large number of diagnostic tests and procedures must be available to those working in the field of oral medicine. The advantages of close association with specialized departments, such as those of clinical immunology, haematology, microbiology, clinical chemistry, gastroenterology, and dermatology, are evident, and virtually all centres in which oral medicine clinics are successfully conducted enjoy such associations. Although the range of investigations carried out in the oral medicine clinic itself may be wide, it is evident that, in many instances, it is proper to refer the patient to a colleague in some other speciality for subsequent investigation following initial diagnosis in the oral medicine clinic. Some units will have special interest or expertise in certain diseases and may be able to offer sophisticated investigations and integrated multidisciplinary care that is not routinely available in all oral medicine clinics.

The importance of taking a patient's temperature when there is a disseminated infection should not go unmentioned. This will indicate if there are any systemic effects from the infection.

Special investigations will be discussed subsequently. However, it is helpful to present an overview of the tests in this lecture. It should be remembered that very few special investigations provide a definitive diagnosis. It is more usual for the results of several investigations to be combined with the clinical history and presentation before a definitive diagnosis can be made. The most common laboratory investigation requested in the oral medicine clinic is a screening procedure for possible blood abnormalities. In view of its widespread application this merits preliminary discussion.

What to consider in patients assessment

History	**Investigations**
Complaint and history	Haematology
Full medical history	Clinical Chemistry
Specific questions	Immunology
Skin involvement	Endocrine studies
Eye problems	Urinalysis
Genital symptoms	Biopsy
Gut problems	Microbiology
Drug history	Imaging
Social history (lifestyle)	Plain radiographs
Tobacco	Salivary gland imaging
Alcohol	CT scan
	MR scan
	Ultrasound
Clinical examination	Blood pressure
Extra-oral	Body Temperature
Intra-oral	Biochemistry

Blood examination

The assessment of oral medicine patients often involves haematological, biochemical, and serological investigations. These tests may be done either as screening tests to help in the diagnosis of some unidentified condition or to confirm a diagnosis by the application of specific tests. In the first instance it may be helpful to categorize tests generically according to the department that performs the investigation.

Haematology

As a screening procedure for possible haematological abnormality, a haemoglobin estimation, white cell count, and blood film examination were once considered to be sufficient. Oral signs and symptoms may, however, accompany relatively minor changes in the blood and oral lesions may occur early in patients with haematological abnormalities, well before these are shown up by the simple examination of peripheral blood. A significant lowering of serum or red cell folate levels or (less frequently) lowered serum B_{12} levels may occur in the absence of any detectable change in the peripheral erythrocytes, particularly in patients with stomatitis and recurrent ulceration. It therefore follows that the simple full blood count is an insufficient procedure for the initial investigation of such patients. Haematology reports (and also those of other investigations) should be interpreted with the aid of the normal values of the laboratory involved. In the case of borderline results of clinical significance it is recommended that a second sample should be taken if at all possible, laboratory figures are subject to some degree of variation. It must be repeated that such results should always be interpreted in the light of the age of the patient and the normal values given by the laboratory involved.

A significant proportion of patients attending the oral medicine clinic will require full haematological screening. It is suggested that the following groups warrant this extended screening procedure:

- patients with recurrent apthous stomatitis
- patients with a persistently sore and/or dry mouth.
- patients with oral lesions with an atypical history or unusually resistant to treatment;
- patients complaining of a sore or burning mouth or tongue, or abnormal taste sensation, even though no mucosal changes can be seen;
- all patients with persistent orofacial candidosis.
- Patients showing abnormalities following an initial screening (i.e. haemoglobin and full blood count).

Haematological screening protocol

When a screening procedure is decided upon, a reasonable scheme of investigation is as follows:

- Full blood count and film examination. From this, evident anaemias are demonstrated by variations in red cell morphology and lowered haemoglobin values. Abnormalities of the white cells and platelet numbers are also shown. Haematological indices such as the red and white blood cell counts, the mean corpuscular haemoglobin, mean corpuscular volume, the haematocrit and platelet count are important and abnormal values may indicate underlying systemic disease.
- Estimation of serum ferritin as a measure of full body iron status. This test has almost entirely replaced the estimations of serum iron, total iron binding capacity, and saturation formerly used as a screening test, although these are still used in the investigation of complex iron-deficiency states.
- Serum B_{12}, folate and red cell folate estimations. These are valuable indicators of malabsorption and, hence, of gastrointestinal diseases of many kinds. The red cell folate level is a relatively stable indicator of folate deficiency, whereas the serum folate levels are more labile and indicate the current status. It has been shown that these may show independent clinically significant variation in patients presenting with oral signs and symptoms. Coeliac disease is an example of a gastrointestinal disease that can result in malabsorption of haematinics. Low folate levels may also be due to anticonvulsant drug therapy, pregnancy, and alcoholism.

  A vitamin B_{12} deficiency should be suspected if there is a macrocytosis indicated by a raised mean corpuscular volume and packed cell volume.

- As an additional test an erythrocyte sedimentation rate (ESR) measurement is useful as a non-specific guide to underlying pathological processes alternatively measurement of C-reactive protein (CRP) may be used as a similar marker for pre-existing disease (see Clinical Immunology). The ESR is raised in pregnancy, chronic inflammatory conditions, acute infection, giant cell arteritis, and neoplasia.

Useful biochemical investigations

Investigation	**Description**
Glucose	Raised in diabetes mellitus, Cushing's syndrome Hypoglycaemia occurs most commonly in diabetic patients and may occur in severe liver disease
Urea	Raised in dehydration, renal failure
Creatinine	Raised in renal failure
Electrolytes	
Sodium	Elevated in dehydration

	Low in conditions causing overhydration, e.g. cardiac failure
Potassium	Raised in renal failure, diabetic ketoacidosis
	Hyperkalaemia is commonly artefactual due to haemolysis, delayed specimens, or ethylenediamine tetraacetic acid (EDTA) contamination
	Hyperkalaemia is a medical emergency and must be corrected immediately
	Hypokalaemia is commonly due to diuretics or gastrointestinal losses of potassium
Calcium	High in primary hyperparathyroidism, malignancy, vitamin D excess
	Low in rickets, osteomalacia, hypoparathyroidism
Phosphate	High in renal failure
	Low in rickets / osteomalacia
Alkaline phosphatase	Raised in conditions with increased bone turnover such as Paget's disease, rickets/osteomalacia
	Also raised in liver disease, particularly cholestasis
Total protein	Raised in dehydration, liver disease, myeloma, connective tissue diseases, and sarcoidosis
	Reduced in overhydration, enteropathy, renal failure
Albumin	Raised in dehydration
	Reduced when there is an acute phase response, e.g. inflammation, postoperatively, carcinoma
	Also raised in severe liver disease, malabsorption, nephrotic syndrome, connective tissue diseases
Ferritin	Raised in liver disease, haemachromatosis, leukaemia
	Reduced in iron deficiency anaemia
Liver enzymes	Disturbed in liver disease, some drug therapies
	Enzyme-inducing drugs, e.g. carbamazepine, phenytoin, phenobarbitone, cause a mild elevation in alkaline phosphatase and Oi glutaryl transferase (OiGT)

Immunological tests

A wide range of immunological tests is available to assist in the diagnosis of diseases affecting the oral cavity and many such tests form an essential part of the diagnostic processes of the oral medicine clinic. Many immunologically based tests are now matters of routine. Others are only available in specialist centres.

Useful immunological tests

Autoantibodies
- Rheumatoid factor
- Antinuclear factor
- SS-A, SS-B antibodies
- Parietal cell antibody
- Anti-gliaden
- Anti-endomysial
- Epithelial intercellular cement
- Epithelial basement membrane

C1 esterase inhibitor (reduced in hereditary angioedema)

Viral antibodies
- HIV
- Epstein-Barr virus

C-reactive protein (raised in inflammation and malignancy)

The assay of circulating autoantibodies is an important procedure in the oral medicine clinic. Some autoantibodies are closely associated with specific disease processes, for instance, gastric parietal cell antibodies with pernicious anaemia. In other autoimmune diseases, however, a wide range of

autoantibodies may be produced. For this reason it is usual to carry out a range of autoantibody tests rather than a single one.

Direct immunofluorescent techniques, for the detection of immunoglobulins and other immunologically active proteins fixed within tissue, have acquired great importance in the diagnosis of oral mucosal lesions particularly those associated with skin diseases and connective tissue disease. The principle of the technique depends on the fact that antibodies combined with fluorescein retain both their immunological activity and the property of the fluorescein to fluoresce under ultraviolet light. The antibodies can, therefore, be located at the exact site of combination with their antigenic antagonists by microscopic observation under ultraviolet illumination. A wide range of highly specific antibodies to the various immunoglobulins and complement components is available and can be used to demonstrate the type and site of bound complexes. In some conditions the results may be highly specific and diagnostic (in pemphigus and pemphigoid, for example). In other conditions (such as lichen planus) they are not clear.

Endocrine function

Endocrine disorders are important in oral medicine for the following reasons.

- Patients may present with a complaint that leads to the diagnosis of an endocrine disturbance. An example is a patient with oral dysaesthesia or xerostomia who upon investigation is found to be an undiagnosed diabetic.
- Poorly controlled hormonal imbalances may lead to orofacial disease.
- Therapy of orofacial disease may lead to hormonal imbalances. An example of this is the use of systemic steroids to treat severe ulceration or bullous disease long-term therapy will induce adrenal suppression and predisposes towards diabetes and osteoporosis.
- Concurrent endocrine disease or hormone replacement therapy may influence the management of the patient.

Examples of hormone studies that may be requested in oral medicine are thyroid function tests and parathormone, growth hormone, and cortisol levels.

Urinalysis

Urinalysis, which can be done quickly and cost-effectively, is used to identify the presence of glucose, blood, proteins, ketones, and bile products. This can alert the clinician to the possibility of underlying systemic disease and, therefore, further investigations will be required. Urine samples are usually collected from the midstream flow avoiding the urine flow at the beginning and end of micturition.

Biopsy

A biopsy involves the removal of part or all of a lesion so that it can be examined by histopathological techniques.

Many lesions may be diagnosed only after examination of an appropriate biopsy specimen of the affected tissue. This is so, not only in cases of suspected neoplasia, but, for example, also in the differential diagnosis of white patches that may occur in the oral mucosa and of the bullous, ulcerative, and desquamative lesions in the mouth. Many bone conditions are, similarly, diagnosed by examination of a biopsy sample. It is generally agreed that, in the case of suspected or possible malignancy of the oral mucosa, biopsy is mandatory and, with simple precautions, is unlikely to cause dissemination of tumour cells. There are several methods of obtaining biopsies and these will be dealt with under the following headings: excisional, incisional, and fine needle aspiration. The decision to take an excisional or incisional biopsy will depend upon the nature of the lesion, its size, and location.

Prior to biopsy the patient should be informed about:

- the reasons for the procedure
- what to expect
- any discomfort

- possible complications

A patient information leaflet is a helpful aid in obtaining informed consent.
Biopsy techniques

- Incisional
- Excisional
- Fine needle aspiration

Excisional biopsy
If the lesion in question is small, it may be best to remove it entirely by local excision, including a small area of normal tissue. The specimen may then be sectioned and its histology reviewed to determine whether further treatment will be needed. The biopsy is far better taken with the knife than with the cutting diathermy, which may cause considerable distortion of the tissues. After its removal, the biopsy specimen should be placed with the minimum of delay into a fixative, 10 per cent formol saline being the most universally used. Full clinical details should always be given to the pathologist who is to examine the specimen.
Excision biopsy is particularly useful for the diagnosis of single small ulcers and small, localized, soft-tissue swellings. In these cases it is possible to combine primary treatment with biopsy.
Incisional biopsy
This is the removal of a section of a lesion for histological study without any attempt being made to remove the whole of the lesion. In taking such a biopsy of the oral soft tissues, the aim should be to include within one specimen, if possible, a clinically typical area of the lesion and also the edge of the lesion. If the choice must be made between the two possibilities, the clinically typical area should be chosen a large area of normal tissue beyond the lesion is quite unnecessary. The specimen should be big enough to allow the pathologist to make a diagnosis, as too small a biopsy is difficult to handle and to orientate for sectioning.
The technique for biopsy of a lesion of the oral epithelium is to make a wedge-shaped cut into the chosen area, to complete the triangle by a third cut, and to then take off the epithelial layer, together with a thickness of corium, by sliding the knife below and parallel with the surface. Even if it is the epithelium that is of particular interest, it is essential that a sufficient layer of corium should be included in order that the subepithelial reactions may be seen. If the biopsy is of a lump, then the wedge section must be taken into the swelling, making sure that any capsular tissue is cut through and that a representative area of the lesion proper is obtained.
Anaesthesia for the biopsy should be obtained by the injection of local anaesthetic as far from the biopsy site as consistent with obtaining a satisfactory result. It is clearly unwise to inject directly into an area of doubtful malignancy and, quite apart from any question of dissemination of neoplastic cells, there is a danger of distortion of the histological picture if the area is infiltrated by anaesthetic. The biopsy site may be closed by one or two sutures.
If the specimen is a thin one, as is often the case with biopsies of the oral mucosa, it is often most convenient to lay it flat on a piece of card or a swab before placing into the fixative. The tissue practically always adheres to this backing, and curling and distortion of the specimen is prevented. Multiple biopsies may be required of large mucosal lesions or in cases with widespread oral lesions that are clinically dissimilar.
Frozen sections for rapid diagnosis are rarely required in oral medicine. Very often the histological sections require careful and detailed study, this being difficult with frozen tissue specimens. Rapid reporting of frozen sections in the urgent situation is possible, for instance, during surgery when it is essential to identify malignancy, but this is not a situation relevant to the regular practice of oral medicine. The major use of frozen sections in oral medicine is in immunofluorescent diagnostic techniques.
Biopsy for immunofluorescence
Antigen antibody complexes in tissues can be identified by various staining and labelling techniques. Fluorescein is a commonly used label. Direct immunofluorescent studies of biopsy

material have become an essential part of the diagnostic procedure for immunobullous oral lesions. In the case of non-bullous and non-erosive lesions there are no particular problems. The specimen is taken from the lesional tissue with some marginal clinically normal tissue if convenient. In the case of bullous or erosive lesions, however, the situation is quite different in that the most characteristic immunological findings are likely to be in the clinically normal tissue adjacent to the lesion. When bulla formation or erosion has occurred, the biopsy technique of the lesion itself becomes very difficult and the results (largely because of secondary infection and similar factors) become much more difficult to interpret.

It is essential when taking biopsy specimens for immunofluorescent studies that the laboratory should be pre-warned so that the fresh, unfixed tissue is passed on directly for immediate processing (or for deep frozen storage). It can be safely transported in a polythene bag or placed on an ice tray. Prior to taking a biopsy the practitioner should decide what type of biopsy is required and what is going to happen to the biopsy specimen. This will prevent unnecessary repeat biopsies.

Both direct and indirect immunofluorescent studies are of value in the diagnosis of immunobullous diseases (for example, pemphigus and pemphigoid).

Fine needle aspiration (FNA) biopsy

Soft-tissue lesions can be collected for microscopic examination using a needle aspirate. This technique is also useful for collecting fluid contents of a lesion, particularly pus or cystic fluid. A 20/21 gauge needle is employed for sampling tissue and ultrasound can be used to guide the positioning of the needle in an attempt to ensure that the biopsy is taken from the centre of the lesion. Sometimes it is not possible to obtain a definitive diagnosis from a FNA biopsy. Often there is enough information to differentiate between malignant and benign. An experienced cytologist is required to interpret the sample and it should be remembered that the specimen harvested may not always be representative of the lesion.

Microbiological investigations

Not all orofacial infections require the services of a diagnostic microbiology laboratory. However, when such services are required, the clinician needs to be aware of the range of services available and the type of specimen required. Laboratories can look for the following evidence of infection.

- Viable organisms. Microorganisms can sometimes be seen microscopically from a direct smear but usually the specimen is cultured. This will then allow the organisms in the culture to be identified and undergo sensitivity testing to antimicrobial agents. For culture and sensitivity testing an aspirate of pus is preferable to a swab. The latter may be contaminated with normal oral flora and the putative pathogens are less likely to survive the journey to the laboratory.
- Microbial products. It is possible to detect the presence of micro-organisms by the products that they produce, such as toxins, or by identifying their DNA. The application of molecular techniques to identify genetic material has allowed for the identification of micro-organisms without the need for culture. Gene amplification using the polymerase chain reaction (PCR) and in situ hybridization techniques allows for the rapid identification of organisms. This is particularly beneficial for organisms that are hazardous or not easily grown in the laboratory. Hepatitis C is identified in this manner.
- Antibody detection. The presence of circulating antibodies in the serum, cerebrospinal fluid (CSF), or in saliva may be indicative of infection. Serological techniques are often employed for viral infections such as hepatitis B.

Bacteriology

If a bacterial aetiology is suspected for a lesion, both direct smears and swabs for culture and identification may be taken. Direct smears from the gingival crevice may be of some value in the identification of the fusobacteria and spirochaetes in acute ulcerative gingivitis although their use is limited. In many instances only normal oral flora will be reported. This is the case, for example, in viral infections. In these circumstances, however, as in many other oral mucosal diseases, the

balance of the oral flora is soon disturbed by the onset of abnormal environmental conditions. When a collection of pus is present an aspirate should ideally be taken.

Mycology

Candida may be recognized on direct smears, by culture, and, if an estimate of density of organisms is required, by imprint culture or an oral rinse. They survive well on a dry swab or when placed in an appropriate transport medium. It must be remembered that in some forms of candidosis, where the organisms are within the tissues (as in chronic hyperplastic candidosis), there may be very little growth from a swab. They are best identified by histological methods. Susceptibility testing to various antifungal agents can be undertaken, but the reproducibility of some tests, particularly those relating to azoles, are questionable.

Virology

Virus identification remains a lengthy and relatively difficult process. Confirmation may be given by direct electron microscopy in the few centres where this is available. Tissue culture, antigen detection, and identification of genetic material are commonly employed techniques.

Serum antibody studies can also form the basis for the diagnosis of viral infections. In herpes simplex the baseline level of antibodies in any individual before clinical infection is variable, depending on the past history and the degree of the immune response. At the time of an active clinical infection these levels are raised considerably. If pairs of sera from the patient, taken at an interval (of about 10 days in this case), can be compared, a significant rise in confirms the diagnosis. Quite clearly, this is not a particularly useful technique, except in retrospect, since, in the case of primary herpetic stomatitis, the lesions will have gone into remission before the confirmation of the diagnosis is available.

Bacteria and viruses can be identified rapidly using molecular techniques such as polymerase chain reaction (PCR) or fluorescent in situ hybridization (FISH).

Imaging techniques

Plain film radiography is the most common imaging technique used in dental practice. The value of plain radiography lies in the simplicity of the method and also the fact that it is widely available. The disadvantages are that ionizing radiation is used and imaging of soft-tissue lesions is often unsatisfactory for most diagnostic purposes. In areas of complex bony anatomy the superimposition of adjacent structures on the region of interest can often limit the diagnostic value of the image. This problem is reduced by the technique of tomography which uses movement of the X-ray tube and film to produce a slice through the patient with blurring of the neighbouring structures. The dental panoramic tomograph (DPT) or panoramic view uses this principle.

Diagnosis

The diagnosis may be obvious from the history and examination of the patient. Further investigations may not be required and the clinician may make a definitive diagnosis.

The clinician may have a strong suspicion of the diagnosis but cannot confirm this until further information is returned, such as a biopsy or blood results. In this situation the practitioner can make a provisional, clinical, or working diagnosis and may start therapy for the suspected condition. It is not uncommon, however, that after examination there remains more than one possible diagnosis. These conditions make up the differential diagnoses. In this situation the clinician needs to assess the likelihood of each differential diagnosis, taking into account the patient's age, gender, and race, the presenting symptoms, the medical and drug history, and the classical features of the various possible diagnoses. This is a skill that becomes defined with experience and requires logical thought and knowledge of the various conditions.

Projects

- Identify the medical and surgical disciplines that specialists in oral medicine may identify closely with and give reasons why these relationships are necessary.
- The participation of an oral medicine specialist in some multidisciplinary (joint) clinics may benefit patient management. What joint clinics do you think would be advisable and list the orofacial conditions that could be managed on these clinics?

Examination of lymph nodes

Lymph nodes may be examined by palpation, ultrasound-guided fine needle aspiration (USG-FNA) and appropriate imaging techniques. Histopathological examination of an excised node is only indicated in specific situations, such as occult primary head and neck tumours and lymphoma.

When examining the lymph nodes of the head and neck, each of the main groups must be palpated in turn, using a systematic approach. From a position behind the patient, the pre-auricular, parotid, facial, submandibular, submental, deep, cervical (upper, mid, and lower), supraclavicular, posterior triangle, and occipital groups of nodes are palpated in turn on each side. When examining the cervical nodes it is helpful to relax the surrounding tissue by bending the patient's head forward and laterally towards the side examined. If a palpable node is found, its texture is noted and it is moved between two fingers to discover any attachment to skin or underlying tissue.

In addition to a detailed extra- and intraoral examination, the examiner should check the skin of the scalp, face, and neck. Plain radiographs of the hard tissues may be required to identify any odontogenic inflammation related to the patient's dentition. Secondary neoplasms in bone usually present as an ill-defined radiolucency. If there are no foci of infection or evidence of mucosal lesions responsible for the cervical lymphadenopathy, then the patient should be referred to a maxillofacial (or ENT) surgeon for further examination of the ear, nose, and throat. Flexible nasoendoscopy or rigid oesophagolaryngoscopy may be required, together with specialized imaging techniques such as MRI and ultrasonography.

Acute infections

Lymphadenitis arising from an acute infection such as a periapical abscess or a pericoronitis is usually unilateral. The appearance of the nodes is rapid, and they are soft and are painful when touched. There may be oedema of the soft tissue surrounding the nodes giving the visual impression of greater enlargement than is, in fact, the case. The facial lymph node, lying just anterior to the anterior border of masseter at the level of the occlusal plane, is commonly involved in children.

Chronic lymphadenitis

In chronic infections the affected nodes are firm but may not be tender. In tuberculosis the involved nodes become attached to the skin and this produces the so-called collar stud abscess. In longstanding cases of chronic infection, calcification of a node may present as a solitary hard, nonfixed swelling. More widespread smaller calcifications in the cervical nodes are more common. They are usually discovered incidentally during radiography, are asymptomatic, and cannot be palpated. Widespread lymph node enlargement may be the first clinical sign of infection with the HIV virus the submandibular nodes are often prominently affected.

Xerostomia

Xerostomia is the subjective feeling of oral dryness, which may or may not be associated with hypofunction of the salivary glands. A lack of saliva may be due to either a loss of secretory tissue in the salivary glands, or a disturbance in the secretory innervation mechanism brought about by the action of xerogenic drugs or, much less commonly, by neurological disease. A significant proportion of patients complaining of xerostomia are found, after investigations, to have some systemic factor responsible for the reduction in salivary function. These systemic factors may be associated with a wide range of disease processes (such as renal and endocrine disturbances) but many of these patients suffer from Sjgren's syndrome; this will be discussed in more detail below.

Xerostomia is a symptom that should be investigated because it may be indicative of underlying systemic disease.

Therapeutic radiation to the head and neck region, for the treatment of malignancy, can also cause a marked diminution in salivary flow and severe oral dryness. Patients treated by whole-body radiation (for example, prior to bone marrow transplantation for leukaemia) and those given radioactive iodine (I^{131}) for thyroid cancer can also suffer from xerostomia. Early diminution of salivary flow due to radiation may be due to damage to the blood supply of the glands, but later effects are the result of destruction of the gland's secretory apparatus.

Neurological disease, either central or peripheral, may be responsible for a decrease in the secretomotor stimulation of the salivary gland and, hence, the dryness of the mouth. However, the

most common cause for this is the action of drugs with the site of action being either central or in the autonomic pathway. Groups of drugs implicated as having this kind of action include antihistamines, antihypertensives, and sedatives. However, the more common ones to cause xerostomia are the psychotropic drugs and, in particular, the antidepressants and tranquillizers. Over 400 drugs have been identified as having the potential to cause varying degrees of oral dryness, and the effects may be potentiated in patients taking multiple xerogenic drugs. Drug-related oral dryness should be a reversible side-effect, with resolution occurring following cessation of the drug.

Causes of xerostomia

Developmental
Aplasia or atresia
Salivary gland disease
Sjgren's syndrome (primary, secondary)
Sarcoidosis
HIV infection
Iatrogenic
Drug-induced
Therapeutic irradiation (e.g. external beam radiotherapy, total body irradiation
Graft-versus-host disease
Psychogenic
Oral dysaesthesia
Burning mouth syndrome
Anxiety/depression
Dehydration
Febrile illness
Diabetes mellitus
Diabetes insipidus
Renal failure
Diarrhoea
Alcohol
May cause salivary gland disease, liver disease, and dehydration
Local
Mouth-breathing

Commonly used drugs that cause xerostomia

- Antidepressants
- Antihistamines
- Decongestants
- Antiparkinsonian agents
- Tranquillizers and hypnotics
- Antipsychotics
- Diuretics
- Appetite suppressants

Salivary hypofunction can also be due to an underlying cognitive disorder, such as depression or chronic anxiety. The ability of acute anxiety to cause a transient reduction in salivary flow is well known to students taking examinations and those engaged in public speaking. Patients with a sensory or cognitive disorder may also have a perception of oral dryness, but objective measurements of salivary flow may be normal and the mouth apparently moist. These individuals

frequently complain of other symptoms, such as a bad taste and abnormal sensations in the mouth. Xerostomia is frequently reported by patients with burning mouth syndrome.
There are conflicting reports on the effect of age on salivary gland function, but there is some evidence that stimulated salivary flow rates are unimpaired with age in healthy, unmedicated individuals. Unstimulated whole salivary flow rates, however, have been shown to decrease with age in healthy non-medicated subjects. Age, in addition to drugs and disease, is important in reducing the secretion of resting whole saliva. Iatrogenic causes and systemic disease are risk factors for xerostomia that are more likely to be encountered in the middle-aged or elderly population.

Questionnaire to identify patients with salivary gland hypofunction

1. Does the amount of saliva in your mouth feel too little, too much or do you not notice it?
2. Does your mouth feel dry when you eat a meal?
3. Do you frequently sip liquids when you eat a meal?
4. Do you have difficulties swallowing any foods?

Signs and symptoms suggestive of salivary gland hypofunction

Symptoms reported
Oral dryness
Burning, tingling sensation of tongue
The need for frequent drinks to be taken whilst eating or talking
Difficulty in chewing and swallowing dry foods
Altered taste (dysguesia) and smell
Recurrent salivary gland swellings/infections
Increase in rate of dental decay
Dry, sore, cracked lips and angles of mouth
Difficulty in talking (dysphonia)
Generalized mucosal soreness and ulceration of denture-bearing areas
Oral examination reveals
Swollen salivary glands
Absence of salivary film over oral mucosa
Dry, paper-thin parchment appearance of oral mucosa or appearance of small amounts of frothy saliva in an otherwise dry mouth
Fissuring and lobulation of the tongue
Dry, cracked lips, angular cheilitis
Evidence of chronic oral candidosis
Development of new carious lesions, especially on incisal or cuspal surfaces

Excessive saliva

An increased salivary flow rate is also known as sialorrhoea or ptyalism and, in contrast to xerostomia, it is an uncommon complaint. Hypersalivation may be transient or a chronic problem. There are several reasons why patients may complain of an increase in the production of saliva, but they are due to two main causes: hypersecretion and neuromuscular dysfunction. Excessive saliva is a frequent complaint of patients who are wearing an intraoral prosthesis for the first time. In fact, one of the commonly used methods of stimulating salivary flow for experimental purposes is to use an inert foreign body within the mouth. Most patients eventually become used to their new dentures or appliance and during this process the excess salivary flow usually disappears. In a few patients, however, this may prove an intractable problem. Infected or ulcerative lesions in the mouth may temporarily cause an increase in salivary flow, which adds to the discomfort of the initial condition. This can be a feature of primary herpetic gingivostomatitis. A similar effect is often seen in carcinoma of the mouth, in which the increased salivary flow may be accompanied by a reduced swallowing reflex and a constant dribbling of saliva. It can be difficult to distinguish between hypersalivation and drooling the terms are not synonymous. In patients with hypersalivation saliva

is normally cleared from the mouth by swallowing. Drooling occurs due to a failure to swallow saliva and is common in infants and also in those with poor neuromuscular coordination. Drooling is not necessarily caused by an overproduction of saliva, but it can occur because of it.
Very few drugs induce excessive salivation, a stark contrast to the number of drugs that reduce salivary flow rate. Anticholinesterases, which enhance neuromuscular transmission and are used in the treatment of myasthenia gravis, can cause hypersalivation. Interestingly, the antipsychotic drug clozapine has been implicated in causing a dry mouth and hypersalivation.

Excessive salivation may be due to:

- hypersecretion (for example, the provision of a new intraoral prosthesis, drugs)
- neuromuscular dysfunction (for example, cerebral palsy)
- oral dysaesthesia (patients with oral dysaesthesia are more likely to report xerostomia)

Systemic conditions, most notably neurological disturbances such as parkinsonism, cerebral palsy, and epilepsy, can cause patients to complain of excessive salivation. In these situations there may be no increase in the production of saliva but swallowing is uncoordinated and inefficient. Mercury poisoning and rabies are extremely rare diseases that have hypersalivation as a symptom.
Treatment for excessive salivation depends largely on the elimination of (or habituation to) the causative factor, whether it be a foreign body or an infective lesion. The use of drugs to suppress salivary flow is rarely indicated since virtually all drugs with a marked salivary suppressive effect also exert other, and often more significant, effects. Anticholinergic drug therapy is sometimes used in patients with cerebral palsy who drool excessively. One frequent oral side-effect of such medication is an increase in caries rate often in a previously caries-free dentition. Alternatively, the major salivary gland ducts can be redirected to the oropharynx to treat drooling. In a few patients complaining of excessive salivation no increase in flow rate can be detected. In this situation there may be an underlying cognitive or psychiatric disturbance, and, indeed, some patients may display obsessional traits. The clinician can reassure the patient that there is no serious morbidity associated with this condition and sialometry may be helpful in demonstrating salivary flow rates within the normal range. In a minority of patients, behavioural therapy may be beneficial.

LECTURE 2

TRAUMATIC INJURIES. MECHANICAL TRAUMA. LEUKOPLAKIA. CHEMICAL AND PHYSICAL TRAUMA. RADIATION SICKNESS.

TRAUMATIC INJURIES

Mechanical trauma

LINEA ALBA

Linea alba ("white line") is a common alteration of the buccal mucosa that is most likely associated with pressure, frictional irritation, or sucking trauma from the facial surfaces of the teeth. In one study of 256 young men, the alteration was present in 13%. No other associated problem, such as insufficient horizontal overlap or rough restorations of the teeth, is necessary for the development of linea alba.

Clinical Features

As the name implies, the alteration consists of a white line that is usually bilateral. It may be scalloped and is located on the buccal mucosa at the level of the occlusal plane of the adjacent teeth. The line varies in prominence and is usually restricted to dentulous areas. It often is more pronounced adjacent to the posterior teeth.

Histopathologic Features

Biopsy is rarely indicated. If a biopsy is performed, hyper-orthokeratosis is seen overlying otherwise normal oral mucosa. On occasion, intracellular edema of the epithelium and mild chronic inflammation of the underlying connective tissue may be noted.

Treatment and Prognosis

No treatment is required for patients with linea alba, and no difficulties are documented as a result of its development. Spontaneous regression may occur.

MORSICATIO BUCCARUM (CHRONIC CHEEK CHEWING)

Morsicatio buccarum is a classic example of medical terminology gone astray; it is the scientific term for chronic cheek chewing. *Morsicatio* comes from the Latin word *morsus,* or bite. Chronic nibbling produces lesions that are most frequently located on the buccal mucosa; however, the labial mucosa **(morsicatio labiorum)** and the lateral border of the tongue **(morsicatio linguarum)** also may be involved. Similar changes have been seen as a result of suction and in glassblowers whose technique produces chronic irritation of the buccal mucosa.

A higher prevalence of classic morsicatio buccarum has been found in people who are under stress or who exhibit psychologic conditions. Most patients are aware of their habit, although many deny the self-inflicted injury or perform the act subconsciously. The occurrence is twice as prevalent in women and three times more prevalent after age 35. At any given time, one in every 800 adults has active lesions.

Clinical Features

Most frequently, the lesions in patients with morsicatio are found bilaterally on the buccal mucosa. They also may be unilateral, combined with lesions of the lips or the tongue, or isolated to the lips or tongue. Thi shredded white areas are infrequently combined intervening zones of erythema, erosion, or foe matic ulceration. The areas of white mucosa demonstrate an irregular ragged surface, and the patient may describe being able to remove of white material from the involved area.

The altered mucosa is typically located in the portion of the anterior buccal mucosa along the c plane. Large lesions may extend some distance a below the occlusal plane in patients whose habit involves pushing the cheek between the teeth with a finger.

Histopathologic Features
Biopsy reveals extensive hyperparakeratosis tha results in an extremely ragged surface with nur projections of keratin. Surface bacterial colonization is typical. On occasion, clusters of vacuolated cells are present in the superficial portion of the prickle cell layer. This histopathologic pattern is not pathognomonic of morsicatio and may bear a striking resemblance to **oral hairy leukoplakia** (OHL), a lesion that most often occurs in people who are infected with the **human immunodeficiency virus** (HIV) or to **uremic stomatitis**. A similar histopathologic pattern is noted in patients who chronically chew betel quid and has been termed **betel chewer's mucosa**. Similarities with linea alba and leukoedema also may be seen.

Diagnosis
In most cases the clinical presentation of morsicatio buccarum is sufficient for a strong presumptive diagnosis, and clinicians familiar with these alterations rarely perform biopsy. Some cases of morsicatio may not be diagnostic from the clinical presentation, and biopsy may be necessary. In patients at high risk for HIV infection with isolated involvement of the lateral border of the tongue, further investigation is desirable to rule out HIV-associated OHL.

Treatment and Prognosis
No treatment of the oral lesions is required, and no long-term difficulties arise from the presence of the mucosal changes. For patients who desire treatment, an oral acrylic shield that covers the facial surfaces of the teeth may be constructed to eliminate the lesions by restricting access to the buccal and labial mucosa. Several authors also have suggested psychotherapy as the treatment of choice, but no extensive well-controlled studies have indicated benefits from this approach.

TRAUMATIC ULCERATIONS

Acute and chronic injuries of the oral mucosa are frequently observed. Injury can result from mechanical damage, such as contact with sharp foodstuffs or accidental biting during mastication, overzealous tooth-brushing, talking, or even sleeping. Some are self-induced and clinically obvious or subtle and difficult to diagnose. Damage also may result from thermal, electrical, or chemical burns. (Oral mucosal manifestations of such burns are discussed later in the chapter.)
Acute or chronic trauma to the oral mucosa may result in surface ulcerations. The ulcerations may remain for extended periods of time, but most usually heal within days. A histopathologically unique type of chronic traumatic ulceration of the oral mucosa is the **eosinophilic ulceration (traumatic granuloma, traumatic ulcerative granulomawith stromal eosinophilia [TUGSE], eosinophilic granuloma of the tongue),** which exhibits a deep pseudoinvasive inflammatory reaction and is typically slow to resolve. Lesions microscopically similar to eosinophilic ulceration have been reproduced in rat tongues after repeated crushing trauma and in traumatic lesions noted in patients with familial dysautonomia, a disorder characterized by indifference to pain. In addition, similar sublingual ulcerations may occur in infants as a result of chronic mucosal trauma from adjacent anterior primary teeth, often associated with nursing. These distinctive ulcerations of infancy have been termed **Riga-Fede disease** and should be considered a variation of the traumatic eosinophilic ulceration. In rare instances, an eosinophilic ulceration is not associated with trauma, demonstrates an inflammatory infiltrate that suggests a neoplastic process, and has been termed **atypical eosinophilic ulceration (atypical histiocyticgranuloma).** Although the term *atypical histiocytic granuloma* was initially coined, several subsequent investigations have shown that the atypical cells often are T-lymphocytes, not histiocytes. The true nature of this alteration is controversial. Although the lesions may undergo spontaneous remission after incisional biopsy, recurrence unrelated to trauma is common. Some investigators have suggested this pattern of eosinophilic ulceration represents the oral counterpart of a cutaneous lymphoproliferative disorder of T-cells that also exhibits sequential ulceration, necrosis, and self-regression.In most cases of traumatic ulceration, there is an adjacent source of irritation, although this is not present invariably.

The clinical presentation often suggests the cause, but many cases resemble early ulcerative squamous cell carcinoma; biopsy is performed to rule out that possibility.

Clinical Features

Some intraoral injuries are intentional and used to attract attention, but the majority of injuries are unintentional from a variety of causes. As would be expected, simple chronic traumatic ulcerations occur most often on the tongue, lips, and buccal mucosa - sites that may be injured by the dentition. Lesions of the gingiva, palate, and mucobuccal fold may occur from other sources of irritation. Overzealous tooth-brushing can create linear erosions along the free gingival margins. Although these areas may superficially resemble a number of the chronic vesiculo-erosive processes, thorough questioning of the patient often leads to the appropriate diagnosis. The individual lesions appear as areas of erythema surrounding a central removable, yellow fibrinopurulent membrane. In many instances, the lesion develops a rolled white border of hyperkeratosis immediately adjacent to the area of ulceration.

Eosinophilic ulcerations are not uncommon but frequently are not reported. The lesions occur in people of all ages, with a significant male predominance. Most have been reported on the tongue, although cases have been seen on the gingiva, buccal mucosa, floor of mouth, palate, and lip. The lesion may last from 1 week to 8 months. The ulcerations appear very similar to the simple traumatic ulcerations; however, on occasion, underlying proliferative granulation tissue can result in a raised lesion similar to a pyogenic granuloma.

Riga-Fede disease typically appears between 1 week and 1 year of age. The condition often develops in association with natal or neonatal teeth. The anterior ventral surface of the tongue is the most common site of involvement, although the dorsal surface also may be affected. Ventral lesions contact the adjacent mandibular anterior incisors; lesions on the dorsal surface are associated with the maxillary incisors. The atypical eosinophilic ulceration occurs in older people, with most cases developing in patients over age 40. Surface ulceration is present, and an underlying tumefaction also is seen. The tongue is the most common site, although the gingiva, alveolar mucosa, mucobuccal fold, buccal mucosa, and lip may be affected.

Histopathologic Features

Simple traumatic ulcerations are covered by a fibrir purulent membrane that consists of fibrin intermixed with neutrophils. The membrane is of variable thickness. The adjacent surface epithelium may be normal or m demonstrate slight hyperplasia with or without hyperkeratosis. The ulcer bed consists of granulation tissue that supports a mixed inflammatory infiltrate of lymphocytes, histiocytes, neutrophils, and, occasionally, plasma eel In patients with eosinophilic ulcerations, the pattern very similar; however, the inflammatory infiltrate extends into the deeper tissues and exhibits sheets of lymphocytes and histiocytes intermixed with eosinophils. In addition the vascular connective tissue deep to the ulceration may, become hyperplastic and cause surface elevation.

Atypical eosinophilic ulcerations exhibit numerous features of the traumatic eosinophilic ulceration, but the deeper tissues are replaced by a highly cellular proliferation of large lymphoreticular cells. The infiltrate is pleomorphic, and mitotic features are somewhat common. Intermixed with the large atypical cells are mature lymphocytes and numerous eosinophils. Although an associated immunohistochemical profile has been rarely reported, investigators have shown the large cells to be T-lymphocytes, the majority of which react with CD30 (Ki-1). This same marker also reacts with the proliferative cells noted in a group of nonaggressive cutaneous lymphomas.

Treatment and Prognosis For traumatic ulcerations that have an obvious source of injury, the irritating cause should be removed. Dyclonine HCl or hydroxypropyi cellulose films can be applied for temporary pain relief. If the cause is not obvious or if a patient I does not respond to therapy, biopsy is indicated. Rapid I healing after a biopsy is typical even with large eosinophilic ulcerations. Recurrence is not expected.

The use of corticosteroids in the management of traumatic ulcerations is controversial. Some clinicians have suggested that use of such medications may delay healing. In spite of this, other investigators have reported success using corticosteroids to treat chronic traumatic ulcerations.

Although extraction of the anterior primary teeth is not recommended, this procedure has resolved the ulcerations in Riga-Fede disease. The teeth should be retained if they are stable. Grinding the incisal mamelons, coverage of the teeth with a light-cured composite or cellulose film, construction of a protective shield, or discontinuation of nursing have been tried with variable success.

Patients with atypical eosinophilic ulcerations should be thoroughly evaluated for evidence of lymphoma elsewhere. Although recurrence is frequently seen, no dissemination of the process has been documented, and all ulcerations reportedly have healed after initial incisional biopsy. Further documentation is critical to define more fully this poorly understood process.

LEUKOPLAKIA (LEUKOKERATOSIS; ERYTHROLEUKOPLAKIA)

Oral leukoplakia *(leuko* = white; *plakia* = patch) is defined by the World Health Organization (WHO) as "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease." The term is strictly a clinical one and does not imply a specific histopathologic tissue alteration.

The definition of leukoplakia is unusual in that it makes the diagnosis dependent not so much on definable appearances as on the *exclusion* of other entities that appear as oral white plaques. Such lesions as lichen planus, morsicatio (chronic cheek nibbling), frictional keratosis, tobacco pouch keratosis, nicotine stomatitis, leukoedema, and white sponge nevus must be ruled out before a clinical diagnosis of leukoplakia can be made. As with most oral white lesions, the clinical color results from a thickened surface *keratin* layer (which appears white when wet) or a thickened *spinous* layer, which masks the normal vascularity (redness) of the underlying connective tissue.

Although leukoplakia is not associated with a specific histopathologic diagnosis, it is typically considered to be a precancerous or premalignant lesion. When the outcome of a large number of leukoplakic lesions is reviewed, the frequency of transformation into malignancy is greater than the risk associated with normal or unaltered mucosa. Because there is considerable misunderstanding of this concept, Box 10-3 provides definitions that are used throughout the chapter.

Incidence and Prevalence

Although leukoplakia is considered a premalignant lesion, the use of the clinical term in no way suggests that histopathologic features of epithelial dysplasia are present in all lesions. Dysplastic epithelium or frankly invasive carcinoma is, in fact, found in only 5% to 25% of biopsy samples of leukoplakia. The precancerous nature of leukoplakia has been established, not so much on the basis of this association or on the fact that more than one third of oral carcinomas have leukoplakia in close proximity, as on the results derived from clinical investigations that followed numerous leukoplakic lesions for long periods. The latter studies suggest a malignant transformation potential of 4% (estimated lifetime risk). Specific clinical subtypes or phases, mentioned later, are associated with potential rates as high as 47%. These figures may be artificially low because many lesions are surgically removed at the beginning of follow-up.

Leukoplakia is by far the most common oral precancer, representing 85% of such lesions. It also is relatively common, with some studies suggesting that it affects as many as 3% of white adults. There is a strong male predilection (70%), except in regional populations in which women use tobacco products more than men. A slight decrease in the proportion of affected males, however, has been noted over the past half century. The disease is diagnosed more frequently now than in the past, probably because of an enhanced awareness on the part of health professionals (rather than because of a real increase in frequency).

Etiology

The cause of leukoplakia remains unknown, although hypotheses abound:

Tobacco. The habit of tobacco smoking appears most closely associated with leukoplakia development. More than 80% of patients with leukoplakia are smokers. When large groups of adults are examined, smokers are much more likely to have leukoplakia than nonsmokers. Heavier smokers have greater numbers of lesions and larger lesions than do light smokers, especially after many years of tobacco use. Also, a large proportion of leukoplakias in persons who stop smoking either disappear or become smaller within the first year of habit cessation.

The smokeless tobacco habit produces a somewhat different result. It often leads to a clinically distinctive white oral plaque called tobacco pouch keratosis. This lesion probably is not a true leukoplakia.

Alcohol. Alcohol, which seems to have a strong synergistic effect with tobacco relative to oral cancer production, has not been associated with leukoplakia. People who excessively use mouth rinses with an alcohol content greater than 25% may have grayish buccal mucosa plaques, but these are not considered true leukoplakia.

Sanguinaria. Persons who use toothpaste or mouti" rinses containing the herbal extract, sanguinaria, may develop a true leukoplakia. This type of leukoplakia (sanguinaria-associated keratosis) is usually located in the maxillary vestibule or on the alveolar mucosa of the maxilla. More than 80% of individuals with vestibular or maxillary alveolar leukoplakia have a history of using products that contain sanguinaria, compared with 3% of the normal population.

The affected epithelium may demonstrate dysplasia identical to that seen in other leukoplakias, although the potential for the development of cancer is uncertain. The leukoplakic plaque may not disappear even after the patient stops using the product; some lesions have persisted for years afterwards.

Ultraviolet radiation. Ultraviolet radiation is accepted as a causative factor for leukoplakia of the lower lip vermilion. This is usually associated with actinic cheilosis. Immunocompromised persons, especially transplant patients, are especially prone to the development of leukoplakia and squamous cell carcinoma of the lower lip vermilion.

Microorganisms. Several microorganisms have been implicated in the cause of leukoplakia. *Treponema pallidum,* for example, produces glossitis in the late stage of syphilis, with or without the arsenic therapy in popular use before the advent of modern antibiotics. The tongue is stiff and frequently has extensive dorsal leukoplakia.

Tertiary syphilis is rare today, but oral infections by another microorganism, *Candida albicans,* are not. *Candida* can colonize the superficial epithelial layers of the oral mucosa, often producing a thick, granular plaque with a mixed white and red coloration. The terms candidal leukoplakia and candidal hyperplasia have been used to describe such a lesion, and biopsy may show dysplastic or hyperplastic histopathologic changes. It is not known whether this yeast produces dysplasia or secondarily infects previously altered epithelium, but some of these lesions disappear or become less extensive, even less severely dysplastic, after antifungal therapy. Tobacco smoking may cause the leukoplakia and also predispose the patient to develop candidiasis.

Human papillomavirus (HPV), in particular subtypes 16 and 18, has been identified in some oral leukoplakias. These are the same HPV subtypes associated with uterine cervical carcinoma and a subset of oral squamous cell carcinomas, Such viruses, unfortunately, also can be found in normal oral epithelial cells, and so their presence is perhaps no more than coincidental. It may be significant, however, that HPV-16 has been shown to induce dysplasia-like changes in normally differentiating squamous epithelium in an otherwise sterile *in vitro* environment.

Trauma. Several keratotic lesions, which until recently had been viewed as variants of leukoplakia, are now considered not to be precancers. Nicotine stomatitis is a generalized white palatal alteration that seems to be a hyperkeratotic response to the heat generated by tobacco smoking rather than a response to the carcinogens within the smoke. Its malignant transformation potential is so low as to be about the same as that of normal palatal mucosa.

In addition, chronic mechanical irritation can produce a white lesion with a roughened keratotic surface, termed frictional keratosis. Although the resulting lesion is clinically similar to true

leukoplakia, such a lesion is now thought to be no more than a normal hyperplastic response (similar to a callus on the skin). Keratoses of this type are readily reversible after elimination of the trauma, and such obviously traumatic lesions as linea alba, morsicatio, and toothbrush gingival "abrasion" have never been documented to have transformed into malignancy, nor does the presence of dentures or broken and missing teeth increase the cancer risk. Frictional keratosis should be differentiated from the group of oral precancers.

Clinical Features

Leukoplakia usually affects persons older than 40 years of age. Prevalence increases rapidly with age, especially for males, and as many as 8% of men older than 70 years of age reportedly are affected. The average age of affected persons (60 years) is similar to the average age for patients with oral cancer; however, in some studies leukoplakia has been found to occur about 5 years earlier (on average) than oral squamous cell carcinoma.

Approximately 70% of oral leukoplakias are found on the lip vermilion, buccal mucosa, and gingiva. Lesions on the tongue, lip vermilion, and oral floor, however, account for more than 90% of those that show dysplasia or carcinoma. Individual lesions may have a varied clinical appearance and tend to change over time. Early and mild lesions appear as slightly elevated gray or gray-white plaques, which may appear somewhat translucent, fissured, or wrinkled and are typically soft and flat. They usually have sharply demarcated borders but occasionally blend gradually into normal mucosa.

Mild or thin leukoplakia, which seldom shows dysplasia on biopsy, may disappear or continue unchanged. For tobacco smokers who do not reduce their habit, as many as two thirds of such lesions slowly extend laterally, become thicker, and acquire a distinctly white appearance. The affected mucosa may become leathery to palpation, and fissures may deepen and become more numerous. At this stage or phase, the lesion is often called a homogeneous or thick leukoplakia. Most thick, smooth lesions remain indefinitely at this stage. Some, perhaps as many as one third, regress or disappear; a few become even more severe, develop increased surface irregularities, and are then called granular or nodular leukoplakia. Some lesions demonstrate sharp or blunt projections and have been called verrucous or verruciform leukoplakia.

A special high-risk form of leukoplakia, proliferative verrucous leukoplakia (PVL), is characterized by the development of multiple keratotic plaques with roughened surface projections. The relationship of PVL to cases described as verrucous leukoplakia is uncertain. The multiple PVL plaques tend to slowly spread and involve additional oral mucosal sites. Although the lesions typically begin as simple, flat hyper-keratoses that are indistinguishable from ordinary leuko-plakic lesions, PVL exhibits persistent growth, eventually becoming exophytic and verrucous in nature. As the lesions progress, they may go through a stage indistinguishable from verrucous carcinoma, but they later usually develop dysplastic changes and transform into full-fledged squamous cell carcinoma (usually within 8 years of initial PVL diagnosis). These lesions rarely regress despite therapy. PVL is unusual among the leukoplakia variants in having a strong female predilection (1:4 male-to-female ratio) and minimal association with tobacco use.

Leukoplakia may become dysplastic, even invasive, with no change in its clinical appearance. However, some lesions eventually demonstrate scattered patches of redness, called erythroplakia. Such areas usually represent sites in which epithelial cells are so immature or atrophic that they can no longer produce keratin. This intermixed red-and-white lesion, called erythroleukoplakia or speckled leukoplakia, represents a pattern of leukoplakia that frequently reveals advanced dysplasia upon biopsy.

Of course, many leukoplakic lesions are a mixture of the previously mentioned phases or subtypes.

In recent years, attempts have been made to develop new techniques to aid in the identification and diagnosis of premalignant and malignant oral lesions. However, at the present time, careful clinical evaluation with directed conventional biopsy remains the best and most accurate means of assessing oral leukoplakic lesions. In their excellent article, Alexander, Wright, and Thiebaud support this approach when they state, "Noninvasive screening techniques such as cytologic testing

(including brush biopsy) and lesion staining with supravital dyes have many pitfalls and should not be considered as substitutes for biopsy when there is concern about malignancy."

Histopathologic Features

Microscopically, leukoplakia is characterized by a thickened keratin layer of the surface epithelium (hyperkeratosis), with or without a thickened spinous layer (acanthosis). Some leukoplakias demonstrate surface hyperkeratosis but show atrophy or thinning of the underlying epithelium. Frequently, variable numbers of chronic inflammatory cells are noted within the subjacent connective tissue.

The keratin layer may consist of parakeratin (hyperparakeratosis), orthokeratin (hyperorthokeratosis), or acombination of both. With parakeratin, there is no granular cell layer and the epithelial nuclei arc retained in the keratin layer. With orthokeratin, the epithelium demonstrates a granular cell layer and the nuclei are lost in the keratin layer.

Verrucous leukoplakia has papillary or pointed surjhce projections, varying keratin thickness, and broad, blunted rete ridges. It may be difficult to differentiate it from early verrucous carcinoma.

PVL shows a variable microscopic appearance, (depending on the stage of the lesions. Early PVL appears as a benign hyperkeratosis that is indistinguishable from other simple leukoplakic lesions. With time, the condition progresses to a papillary, exophytic proliferation that is similar to localized lesions of verrucous leukoplakia (or what is sometimes termed verrucous hyperplasia). In later stages, this papillary proliferation exhibits down growth of well-differentiated squamous epithelium with broad, blunt rete ridges. This epithelium demonstrates invasion into the underlying lamina propria; at this stage, it is indistinguishable from verrucous carcinoma. In the final stages, the invading epithelium becomes less differentiated, transforming into a full-fledged squamous cell carcinoma. Because of the variable clinical and histopathologic appearance of PVL, careful correlation of the clinical and microscopic findings is required for diagnosis.

Most leukoplakic lesions demonstrate no dysplasia on biopsy. Evidence of epithelial dysplasia is found in I only 5% to 25% of cases if all oral sites are considered. I When present, these dysplastic changes typically begin in the basilarand parabasilar portions of the epithelium. The more dysplastic the epithelium becomes, the more the atypical epithelial changes extend to involve the entire thickness of the epithelium. The histopathologic alterations of dysplastic epithelial cells are similar to those of squamous cell carcinoma and may include the following:

• Enlarged nuclei and cells
• Large and prominent nucleoli
• Increased nuclear-to-cytoplasmic ratio
• Hyperchromatic (excessively dark-staining) nuclei
• Pleomorphic (abnormally shaped) nuclei and cells
• Dyskeratosis (premature keratinization of individual cells)
• Increased mitotic activity (excessive numbers of mitoses)
• Abnormal mitotic figures (tripolar or star-shaped mitoses, or mitotic figures above the basal layer)

In addition, histomorphologic alterations of dysplastic epithelium are evident at low-power magnification, including:

• Bulbous or teardrop-shaped rete ridges
• Loss of polarity (lack of progressive maturation toward the surface)
• Keratin or epithelial pearls (focal, round collections of concentrically layered keratinized cells)
• Loss of typical epithelial cell cohesiveness

When epithelial dysplasia is present, the pathologist provides a descriptive adjective relating to its "severity" or intensity. Mild epithelial dysplasia refers to alterations limited principally to the basal and parabasal layers. Moderate epithelial dysplasia demonstrates involvement from the basal layer to the midportion of the spinous layer. Severe epithelial dysplasia demonstrates alterations from the basal layer to a level above the midpoint of the epithelium. Sometimes dysplasia will be seen to extend down the duct of a minor salivary gland, especially in lesions of the floor of the mouth.

When the entire thickness of the epithelium is involved, the term carcinoma *in situ* is used. Carcinoma *in situ* is defined as dysplastic epithelial cells that extend from the basal layer to the surface of the muco'sa ("top-to-bottom" change). There may or may not be a thin layer of keratin on the surface. The epithelium may be hyperplastic or atrophic. This entity is considered by some authorities to be a precancerous lesion;
others believe that it represents a genuine malignancy discovered before invasion. Regardless of the concept preferred, the important feature of carcinoma *in situ* is that no invasion has occurred, despite the fact that the atypical epithelial cells look exactly like those of squa-mous cell carcinoma. Without invasion, the most serious aspect of malignant transformation, metastasis, cannot occur. In this light, it should be mentioned that keratin pearl formation is rare in carcinoma *in situ* and may indicate the presence of a focus of invasive squamous cell carcinoma in the adjacent tissue.

Sometimes dysplasia will be seen extending down the ducts of the minor salivary glands, especially in lesions in the floor of the mouth. When ductal dysplasia occurs in a precancerous surface dysplasia, the recurrence rate is increased. The depth of ductal dysplasia does not appear to be a significant factor.

Treatment *and* Prognosis

Because leukoplakia represents a clinical term only, the first step in treatment is to arrive at a definitive histopathologic diagnosis. Therefore, a biopsy is mandatory and will guide the course of treatment. Tissue obtained for biopsy, moreover, should be taken from the clinically most "severe" areas of involvement (with features toward the right side of. Multiple biopsies of large or multiple lesions may be required. Leukoplakia exhibiting moderate epithelial dysplasia or worse warrants complete destruction or removal, if feasible. The management of leukoplakia exhibiting less severe change is guided by the size of the lesion and the response to more conservative measures, such as smoking cessation.

Complete removal can be accomplished with equal effectiveness by surgical excision, electrocautery, cryosurgery, or laser ablation. Long-term follow-up after removal is extremely important because recurrences are frequent and because additional leukoplakias may develop. This is especially true for the verruciform or granular types, 83% of which recur and require additional removal or destruction.

Leukoplakia not exhibiting dysplasia often is not excised, but clinical evaluation every 6 months is recommended because of the possibility of progression toward epithelial dysplasia. Additional biopsies are recommended if smoking continues or if the clinical changes increase in severity.

Overall, 4% of oral leukoplakias become squamous cell carcinoma after diagnosis, according to follow-up studies. As previously stated, this figure, and those mentioned later, may be artificially low because so many followed cases are treated early in an investigation. Not to do so, of course, raises certain ethical questions; hence, more accurate data may never become available. Other confounding features of leukoplakia follow-up investigations include variations in diagnostic definitions and periods of observation. Typically, the latter extend for 5 to 10 years, but several studies have observed patients with lesions for more than 20 years - one study for more than half a century.
With these caveats in mind, follow-up investigations have demonstrated that carcinomatous transformation usually occurs 2 to 4 years after the onset of the white plaque, but it may occur within months or after decades. Transformation does not appear to depend on the age of the affected patient.

Although dysplasia may be present in any leukoplakia, each clinical appearance or phase of leukoplakia ias a different malignant transformation potential. Thin i leukoplakia seldom becomes malignant without demonstrating a clinical change. Homogeneous, thick leukoplakia undergoes malignant transformation in 1 % to 7% of cases. Once the surface becomes granular or verruciform, the malignant transformation potential becomes 4% to 15%. Erythroleukoplakia carries an average transformation potential of 28%, but the rates have varied from 18% to 47% in different investigations.

The increased frequency of transformation of the different phases of leukoplakia is related closely to the degree of dysplasia present. The greater the clinical severity, the greater the chance of significant dysplasia and malignant transformation. Estimates of the malignant potential for histopathologically proven dysplastic lesions are, unfortunately, open to question because so many are excised completely. Thus, their true biologic behavior in an unaltered state may not be appreciated fully. With this understanding, however, lesions diagnosed as moderate and severe dysplasia reportedly have malignant transformation potentials of 4% to II % and 20% to 35%, respectively. Cancers from dysplastic lesions usually develop within 3 years of the dysplasia diagnosis, but can occur much later. Additionally, one in three dysplasias will recur after complete removal.

In addition to the clinical and histopathologic appearance at diagnosis, several factors may increase the risk for cancer in leukoplakic lesions. These include persistence over several years, occurrence in a female patient, occurrence in a nonsmoker, and occurrence on the oral floor or ventral tongue. Leukoplakia of the latter two locations has shown malignant transformation in 16% to 39% of all cases and 47% of those occurring in females.

Some smoking-related leukoplakias with no or minimal dysplasia may disappear or diminish in size within 3 months after the patient stops smoking. Thus habit cessation is recommended. Chemoprevention also may be useful, but remains primarily experimental. High doses of isotretinoin (13-cis-retinoic acid, a form of vitamin A) followed by a course of low-dose isotretinoin or beta-carotene have been reported to reduce or eliminate some leukoplakic lesions in short-term studies. Toxic reactions to systemic retinoids are frequent, however, as is lesion recurrence after the conclusion of therapy.

ERYTHROPLAKIA (ERYTHROPLASIA; ERYTHROPLASIA OF QUEYRAT)

As with leukoplakia, erythroplakia is defined as a red patch that cannot be clinically or pathologically diagnosed as any other condition. The term *erythroplasia* originally was used by Qyeyrat to describe a precancerous red lesion that develops on the penis. Oral erythroplakia is clinically and histopathologically similar to the genital process. Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma *in situ,* or invasive squamous cell carcinoma. The causes of erythroplakia are unknown, but they are presumed to be the same as those associated with invasive squamous cell carcinoma of the mouth.

The point prevalence rate (number of persons with active lesions at a given point in time) of oral erythroplakia has been estimated as 1 per 2500 adults. The incidence is not known, but the average annual incidence for microscopically proven oral carcinoma *in situ,* which represents the great majority of erythroplakias, has been estimated to be 1.2 per 100,000 population (2.0 in males and 0.5 in females) in the United States.

Erythroplakia also may occur in conjunction with leukoplakia and has been found concurrently with a large proportion of early invasive oral carcinomas. Although erythroplakia is less common than leukoplakia, it has a much greater potential to be severely dysplastic at the time of biopsy or to develop invasive malignancy at a later time.

Clinical Features

Erythroplakia is predominantly a disease of older men, with a peak prevalence at 65 to 74 years. The floor of mouth, tongue, and soft palate are the most common sites of involvement, and multiple lesions may be present.

The altered mucosa appears as a well-demarcated erythematous macule or plaque with a soft, velvety texture. It is usually asymptomatic and may be associated with an adjacent leukoplakia (erythro-leukoplakia). Nonspecific mucositis, candidiasis, psoriasis, or vascular lesions may clinically mimic erythroplakia, and biopsy often is required to distinguish between them.

Histopathologic Features

According to one large clinicopathologic investigation, 90% of erythroplakic lesions histopathologically represent either severe epithelial dysplasia, carcinoma *in situ*, or superficially invasive squamous cell carcinoma. The epithelium shows a lack of keratin production and often is atrophic, but it may be hyperplastic. This lack of keratinization especially when combined with epithelial thinness allows the underlying microvasculature to show through thereby explaining the red color. The underlying connective tissue often demonstrates chronic inflammation.

Treatment and Prognosis

Red lesions of the oral mucosa, especially those of the oral floor and ventral or lateral tongue, should be viewed with suspicion, and a biopsy should be performed. If a source of irritation can be identified and removed, biopsy of such a lesion may be delayed for 2 weeks to allow *a* clinically similar inflammatory lesion time to regress.

As with leukoplakia, the treatment of erythroplakia is guided by the definitive diagnosis obtained by biopsy. Lesions exhibiting moderate dysplasia or worse must be removed completely or destroyed by the methods used for leukoplakia. It is best, however, to preserve most of the specimen for microscopic examination because of the possibility that a focal invasive carcinoma might be missed in the initial biopsy material. Recurrence and multifocal oral mucosal involvement are common with erythroplakia; hence, long-term follow-up is suggested for treated patients.

SMOKELESS TOBACCO USE AND SMOKELESS TOBACCO KERATOSIS (SNUFF POUCH; SNUFF DIPPER'S LESION; TOBACCO POUCH KERATOSIS; SPIT TOBACCO KERATOSIS)

The habit of chewing coarsely cut tobacco leaves (chewing tobacco) or holding finely ground tobacco leaves (snuff) in the mandibular vestibule was once almost universal in the United States and is still common among certain populations around the world, most notably in India and Southeast Asia. Either habit is referred to as smokeless tobacco use or spit tobacco use. The latter term is preferred by the U.S. federal government in its attempt to diminish the appeal of the habit. At present, the proportion of adult men in the United States who regularly use spit tobacco approximates 6%. Among young men it is more than 10%, and the proportion is as high as 21 % in some Southeastern and Midwestern states. The habit is started early in life, usually at 8 to 14 years of age, and rarely is initiated after 20 years of age. A recent national survey detected smokeless tobacco lesions of all types in 1.5% (2.9% in males, 0.1 % in females) of U.S. adolescents and teenagers.

Clinical Features

Several health and addiction hazards may be associated with the use of spit tobacco because of the ready absorption of nicotine and other molecules through the oral mucosa. A variety of local oral alterations also are found in chronic users. One of the most common local changes is a characteristic painless loss of gingival and periodontal tissues in the area of tobacco contact. This gingival "recession" frequently includes destruction of the facial surface of the alveolar bone and correlates well with the quantity of daily use and the duration of the smokeless tobacco habit.

Dental caries also has been reported to be more prevalent in spit tobacco users, perhaps because of the high sugar content of some brands; other reports dispute caries susceptibility. Long-term use may lead to localized or generalized wear of occlusal and incisal surfaces, I especially in persons employed in dusty environments. A brown-black extrinsic tobacco stain is typically found I on the enamel and cementum surfaces of the teeth adjacent to the tobacco. In addition, halitosis is a frequent finding in chronic users.

A characteristic white plaque, the smokeless tobacco keratosis, also is produced on the mucosa in direct con-| tact with snuff or chewing tobacco. In Western cultures, it affects 15% of chewing tobacco users and 60% of snuff I users, if mild examples are included. The development | of this lesion is most strongly influenced by habit duration and also by the brand of tobacco used, early onset, of spit tobacco use, total hours of daily use, amount of tobacco consumed daily, and number

of sites routinely used for tobacco placement. In India, smokeless tobacco I keratosis (which is often mistakenly referred to as leukoplakia) is much more prevalent, presumably because of | the increased hours of daily use and the use of different I tobacco leaves combined in a quid with other products, I such as betel leaves, areca nuts, and slaked lime.

Smokeless tobacco keratosis in many Western cultures is usually noted in young adult men and in men older than 65 years of age, because the habit has not been popular among the generation that is now middle-aged. In some populations, the prevalence of smokeless tobacco keratosis (and the smokeless tobacco habit) is most frequent among older women. Individual lesions begin to develop shortly after heavy tobacco use begins, and new lesions seldom arise in persons with a long history of use. The lesion is confined to areas in direct contact with spit tobacco. It is typically a thin, gray or gray-white, almost "translucent," plaque with a border that blends gradually into the surrounding mucosa. Sometimes mild peripheral erythema is present.

The altered mucosa typically has a soft velvety feel to palpation, and stretching of the mucosa often reveals a distinct "pouch" (snuff pouch, tobacco pouch) caused by flaccidity in the chronically stretched tissues in the area of tobacco placement. Because the tobacco is not in the mouth during a clinical examination, the usually stretched mucosa appears fissured or rippled, in a fashion resembling the sand on a beach after an ebbing tide. Similar alterations can occur when other bulky materials are held chronically in the vestibule (e.g., hard candy). Induration, ulceration, and pain are not associated with this lesion.

Smokeless tobacco keratosis usually takes I to 5 years to develop. Once it occurs, however, the keratosis typically remains unchanged indefinitely unless the daily tobacco contact time is altered. In some cases, the white lesion gradually becomes thickened to the point of appearing leathery or nodular.

Histopathologic Features

The histopathologic appearance of smokeless tobacco keratosis is not specific. The squamous epithelium is hyperkeratinized and acanthotic, with or without intracellular vacuolization or "edema" of glycogen-rich superficial cells. Parakeratin chevrons may be seen as pointed projections above or within superficial epithelial layers. Increased subepithelial vascularity and vessel engorgement often are seen. In some cases, an unusual deposition of amorphous eosinophilic material is noted within the subjacent connective tissue and salivary glands. Epithelial dysplasia is uncommon in smokeless tobacco keratosis and, when present, is typically mild. Occasionally, however, significant dysplasia or squamous cell carcinoma may be present.

Treatment and Prognosis

Chronic use of smokeless tobacco in the United States is considered to be carcinogenic. Fortunately, the clinical appearance of smokeless tobacco keratosis is distinct enough and the malignant transformation potential is low enough so that biopsy is needed for only the more severe lesions (i.e., those demonstrating an intense whiteness, agranular orverruciform clinical appearance, ulceration, mass formation, induration, or hemorrhage). Obviously, treatment would then depend on the histopathologic diagnosis. Without microscopic evidence of dysplasia or malignancy, keratoses are not treated. Alternating the tobacco chewing sites between the left and right sides will eliminate or reduce the keratotic lesion but may result in epithelial alteration or gingival and periodontal difficulties in two sites rather than one.

One U.S. study showed that the risk of developing oral cancer was about four times greater in chronic smokeless tobacco users than in nonusers. Recent studies from Sweden, however, have failed to show an increased risk for users of Swedish moist snuff. On the Indian subcontinent, the long-term risk of oral cancer for betel quid users is much higher (8%); 2% of biopsied keratotic lesions in those users already have evidence of malignancy. Even without tobacco in the betel quid, the risk of malignant transformation is approximately 10 times higher than normal.

Squamous cell carcinoma is the most common malignancy resulting from this habit, but an uncommon and relatively unique low-grade oral malignancy, verrucous carcinoma ("snuff dipper's" cancer), may also be associated with spit tobacco use.

Significantly, habit cessation leads to a normal mucosal appearance (usually within 2 to 6 weeks) in 98% of smokeless tobacco keratosis lesions that are not intensely white. A lesion that remains after 6 weeks without smokeless tobacco contact should be considered to be a true leukoplakia and should be sampled for biopsy and managed accordingly.

Speckled leukoplakia.

This term applies to lesions consisting of white flecks or fine nodules on an atrophic erythematous base. They can be regarded as a combination of or transition between leukoplakia and erythroplasia. Speckled leukoplakia also more frequently shows dysplasia than lesions with a homogeneous surface. The histological characteristics are usually, therefore, intermediate between leukoplakia and erythroplasia.

Many cases of chronic candidosis have this appearance.

CHEMICAL AND PHYSICAL TRAUMA. RADIATION SICKNESS

Physical injury

Acute physical injury can be provoked by the influence of hot water, thermal devices, electric current, momentary influence of large doses of radiation.

Acute pain is the first symptom of acute injury. Afterwards appears the feeling of oral mucous roughness, acute gingivitis develops, epithelium is partly or fully macerated with blister formation turning up to erosions and ulcers.

Treatment of acute physical trauma is the same as in the case of nonspecific acute inflammatory processes.

Galvanic currents.

Galvanic currents in the oral cavity, exceeding 10 mcA are one of the examples of chronic physical injury. Their origin is connected with different metals present in oral cavity. For example gold crowns, silver amalgams, steel, bridges with solder alloys. Patients complains are burning feeling in the mouth and tongue especially, paresthesia, metallic taste in the mouth.

The origin of some diseases (leucoplakia, lichen planus) of oral mucous can be connected with galvanic currents in the oral cavity.

In the case of exceeding galvanic currents in the mouth metallic constructions have to be taken off. Sometimes it is enough to change amalgam fillings.

Chemical injury.

Chemical injuries of the oral mucous are acute and chronic. Acute injuries of the oral mucous are the result of the influence of highly concentrated chemical substances – acids, alkalis, arsenic paste, phenol, formalin, argent nitrate, formalin-resorzin mixure. It is important to distinguish chemical burns with allergic reactions. Allergic reactions and chemical burns can be combined sometimes, especially in the case of chronic chemical trauma. For example when patient uses dentures where plastic is not completely polymerized. Chronic injury occurs usually after the prolonged contact of oral mucous with some chemicals. To stop the toothache patients often use locally some medications (alcohol, acetylsalicylic acid, etc.).

Clinical picture of chemical injury depends on the type of the chemical agent and the time of its exposure to oral mucous. Acid burns lead to the coagulation necrosis with the firm, grayish-brown film (sulfuric acid), yellow colored film (nitric acid) or white and gray film (other acids). This changes are accompanied by the expressed inflammation and edema.

Alkaline burn leads to the colliquation necrosis. It is characterized by the absence of the firm surface and necrotic tissues with jelly-like consistency. Injury is much deeper than in acid burn. Necrosis in these type occupies all layers of oral mucous, especially when being localized on the

gums and hard palate. Burns are extremely painful. Necrotic tissues are resolved in several days exposing ulcers with slow healing capacity.

Treatment of chemical injuries.

After the ingress of chemical substance to the oral mucous the agent has to be washed thoroughly with water or neutralizing solutions of low concentration. In the case of acid, among neutralizing solutions are water with soap, ammonia liquid (15 drops per one glass of water), etc. In the case of the burn caused by the alkaline agents they have to be neutralized with the 0,5% solution of citric acid, acetic acid (one fourth of the teaspoon dissolved in one glass of water). In the case of the argent nitrate burn Lugol's solution or 2-3% solution of NaCl should be use to lower the concentration of the alkali (the reaction leads to the formation of the insoluble salts of argent). In the burns produced by phenol oral mucous has to be treated with 50% alcohol. Further treatment after the neutralization is carried out in the same way as the acute nonspecific inflammatory process. Antiseptic solutions and medications stimulating tissue regeneration are used to promote healing processes in the oral mucous.

Radiation sickness

Radiation sickness develops after influence of different types of irradiation: X-rays, gamma rays, neutron currents.

Changes in the irradiated tissues include: changes of the morphological structures of blood vessels, lowering of the resistance of connective tissue, decreased rate of tissue regeneration.

Radiation sickness can occur in acute and chronic forms.

Acute Radiation sickness developes after one-time large dosage irradiation (100-1000 rad).

Four periods of disease progression can be distinguished.

I period – period of primary reactions (takes place 1-2 hours after the irradiation and lasts up to two days).

Changes in oral cavity include dryness of oral mucosa (or increased salivation), lowered taste, sensitiveness of oral mucosa. Oral mucosa and lips are oedematous with hyperaemia and spot hemorrhages.

II period – latent period, lasts from several hours up to two weeks. This period is caracterized by the disappearance of all the previous symptoms.

III period – period of prominent clinical changes, the peak of the disease progression. Upon numerous general changes and increasing fatigue, canges in oral cavity are characterized as *radiation stomatitis*. Patients suffer from severe constant burning sensation, dryness and anemia of oral mucosa, hemorrhages (due to the blood system and vessels affection). Because of the lowered resistance of the immune system autoinfections (especially anaerobic) are rapidly progressing. Most traumatized areas are involved in the disease – periodontal tissues, tonsillars and then lateral surfaces of the tongue, hard and soft palate. Metal constructions (crown, bridges) can be the souree of secondary irradiation in the mouth.

Gingival tissues become soft, friable, necrotic. Alveolar bone is resorbed leading to teeth mobility. Multiple necrosis of oral mucosa are not demarcated and the inflammatory reaction of adjacent mucosa is weak. The bottom of the ulcers is covered with dark-grey necrotic plague with putrid odor.

In heavy cases necrosis can spreads from the superficial tissues to the underneath layers of oral mucosa and the bone, which leads to the radiation bone necrosis with the formation of the sequesters. Bone fractures can occur in the patients.

The tongue is swollen and covered with massive plaque. Clefts hemorrhages and necrosis of the tongue can occur. Taste and sensitiveness of the tongue usually disappear.

Necrotic tonsillitis are typical for this period of the disease.

IV period – period of disease regression. Relapses of the disease are also possible.

Chronic Radiation sickness

Chronic Radiation sickness develops after the prolonged irradiation of small dosages of radiation.

Oral cavity is susceptible to different types of irradiation.

Dryness of oral mucosa gradually increases due to the affection of salivary glands. Refractory gingivitis turning up to ANUG, erosions and ulcers spreading to oral mucosa and lips are often findings in Chronic Radiation sickness. Glossalgia and glossitis with clefts can occur.

Treatment of Radiation sickness is divided into general and local. General treatment includes the use of medications which decreas radiochemical reactions (radioprotectors) – cystamin, batilol), corticosteroids, antihistamine, antibacterial medications. Remedies improving the function of blood system are recommended (Vit. B_6, B_{12}, Folic acid, Na Nucleinate), antihemorrhagic drugs (vikasol, Ca Gluconate).

Local treatment includes antibacterial therapy and professional oral hygiene under local anesthesia.

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LECTURE 3
VIRAL INFECTIONS OF ORAL MUCOSA.

Herpes simplex virus

Hertpes simplex virus (HSV) is a DNA virus and a member of the human herpesvirus (HHV) family, officially known as Herpetoviridae. Two types of HSVs are known to exist: type I (HSV-1 or HHV-1) and type II (HSV-2 or HHV-2). Other members of the HHV family include varicella zoster virus (VZV or HHV-3), Epstein-Barr virus (EBV or HHV-4), cytomegalovirus (CMV or HHV-5), and several more recently discovered members, HHV-6, HHV-7, and HHV-8. The latter virus, HHV-8, appears to be involved in pathogenesis of Kaposi's sarcoma (KS). Humans are the only natural reservoir, and all HHVs have the ability to reside for life within the infected host. After the initial infection, variable periods of latency and reactivation with viral shedding are seen. Because each affected individual remains a reservoir of infection for life, the viruses are endemic worldwide.

The two types of HSVare similar structurally but different antigenically. In addition, the two exhibit epidemiologic variations.

HSV-1 is spread predominantly through infected salvia or active perioral lesions. HSV-1 is adapted best and performs more efficiently in the oral, facial, and ocular areas. The pharynx, intraoral sites, lips, eyes, and skin above the waist are involved most frequently.

HSV-2 is adapted best to the genital zones, is transmitted predominantly through sexual contact, and typically involves the genitalia and skin below the waist. Exceptions to these rules do occur, and HSV-1 can be seen in a pattern similar to that of HSV-2 and vice versa. The clinical lesions produced by both types are identical, and both produce the same changes in tissue. The viruses are so similar that antibodies directed against one cross-react against the other. Antibodies to one of the types decrease the chance of infection with the other type; if infection does occur, the manifestations often are less severe.

Clinically evident infections with HSV-1 exhibit two patterns. The initial exposure to an individual without antibodies to the virus is called the primary infection. This typically occurs at a young age, often is asymptomatic, and usually does not cause significant morbidity. At this point, the virus is taken up by the sensory nerves and transported to the associated sensory or, less frequently, the autonomic ganglia. With oral HSV-1 infection, the trigeminal ganglion is colonized, and the virus remains at this site in a latent state. The virus uses the axons of the sensory neurons to travel back and forth to the peripheral skin or mucosa.

Secondary, recurrent, or recrudescent HSV-1 infection occurs with reactivation of the virus, although many patients may show only asymptomatic viral shedding in the saliva. Symptomatic recurrences are fairly common and affect the epithelium supplied by the sensory ganglion. Spread to an uninfected host can occur easily during periods of asymptomatic viral shedding or from symptomatic active lesions. When repeatedly tested, approximately one third of individuals with HSV-1 antibodies occasionally shed infectious viral particles, even without active lesions being present. In addition, the virus may spread to other sites in the same host to establish residency at the sensory ganglion of the new location. Numerous conditions such as old age, ultraviolet light, emotional stress, pregnancy, allergy, trauma, respiratory illnesses, menstruation, systemic diseases, or malignancy have been associated with reactivation of the virus, but only ultraviolet light exposure has been demonstrated unequivocally to induce lesions experimentally. More than 80% of the primary infections are purported to be asymptomatic, and reactivation with asymptomatic viral shedding greatly exceeds clinically evident recurrences.

HSV does not survive long in the external environment, and almost all primary infections occur from contact with an infected person who is releasing the virus. The usual incubation period is 3 to 9 days. Because HSV-1 usually is acquired from contact with contaminated saliva or active perioral lesions, crowding and poor hygiene promote exposure. Lower socioeconomic status correlates with earlier exposure. In developing countries, more than 50% of the population is exposed by 5 years of age, 95% by 15 years of age, and almost universal exposure by 30 years of age. On the other hand, upper socioeconomic groups in developed nations exhibit less than 20% exposure at five years of age and only 50% to 60% in adults. The low childhood exposure rate in the privileged groups is followed by a second peak during the college years of life. The age of initial infection also affects the clinical presentation of the symptomatic primary infections. People exposed to HSV-1 at an early age tend to exhibit

gingivostomatitis; those initially exposed later in life often demonstrate pharyngotonsillitis.

As mentioned previously, antibodies to HSV-1 decrease the chance of infection with HSV-2 or lessen the severity of the clinical manifestations. The dramatic increase recently seen in HSV-2 is due partly to lack of prior exposure to HSV-1 and to increased sexual activity and lack of barrier contraception. HSV-2 exposure correlates directly with sexual activity. Exposure of those younger than age 14 is close to zero, and most initial infections occur between the ages of 15 and 35. The prevalence varies from near zero in celibate adults to more than 80% in prostitutes.

In addition to clinically evident infections, HSV ha been implicated in a number of noninfectious processes. More than 15% of cases of erythema multiforme are preceded by a symptomatic recurrence of HSV 3 to 10 days earlier. In some instances, the attacks of erythema multiforme are chronic enough warrant antiviral prophylaxis. An association with cluster headaches and a number of cranial neuropathic has been proposed, but definitive proof is lacking.

On rare occasions, asymptomatic release of HSV will coincide with attacks of aphthous ulcerations. The ulcerations are not infected with the virus. In these rare cases, the virus may be responsible for the initiation of the autoimmune destruction; conversely, the immune regulation that produces aphthae may have allowed the release of the virions. In support of the lack of association between HSV and aphthae in the general population of patients with aphthous ulcerations, prophylactic oral acyclovir does not decrease the recurrence rate of the aphthous ulcerations. Although the association between HSV and recurrent aphthous ulcerations is weak, it ma be important in small subsets of patients.

HSV also has been associated with oral carcinomas, but much of the evidence is circumstantial. The DNA form HSV has been extracted from the tissues of some tumors but not from others. HSV may aid carcinogenesis through the promotion of mutations, but the oncogenic role, if any, is uncertain.

Clinical Features

Acute herpetic gingivostomatitis is the most common pattern of symptomatic primary HSV infection, and more than 90% are the result of HSV-1. In a study of more than 4000 children with antibodies to HSV-1, Juretic found that only 12 % of those infected had clinical symptoms and signs severe enough to be remembered by the affected children or their parents. In spite of this stud some health care practitioners suspect that the percentage of primary infections that exhibit clinical symptoms is much higher. Further studies are needed to fully answer this question.

Most cases of acute herpetic gingivostomatitis ari between the ages of 6 months and 5 years, with the peak prevalence occurring between 2 and 3 years of age. I spite of these statistics, occasional cases have be reported in patients over 60 years of age. Development before 6 months of age is rare because of protection I maternal anti-HSV antibodies. The onset is abrupt an often accompanied by anterior cervical lymphadenopathy, chills, fever (103° to 105° F), nausea, anorexia, irritability, and sore mouth lesions. The manifestations vary from mild to severely debilitating.

Initially the affected mucosa develops numerous pin-1 vesicles, which rapidly collapse to form numerous all, red lesions. These initial lesions enlarge slightly I develop central areas of ulceration, which are covered by yellow fibrin. Adjacent ulcerations coalesce to form larger, shallow, irregular ulcerations. Both the movable and attached oral mucosa can be affected, and the number of lesions is highly variable. In all cases, the gingiva is enlarged, painnful, and extremely erythematous. In addition, the affected gingiva often exhibits distinctive punched-out erosions along the midfacial free gingival margins. It is not unusual for the involvement of the labial mucosa to extend past the wet line to include the adjacent vermilion border of the lips. Satellite vesicles of the perioral skin are fairly common. Self-inoculation of the fingers, eyes, and genital areas can occur. Mild cases usually resolve within 5 to 7 days; severe cases may extend to 2 weeks.

As mentioned previously, when the primary infection occurs in adults, some symptomatic cases exhibit **pharyngotonsillitis.** Sore throat, fever, malaise, and headache are the initial symptoms. Numerous small vesicles develop on the tonsils and posterior pharynx. The vesicles rapidly rupture to form numerous shallow ulcerations, which often coalesce with one another. A diffuse, grayish-yellow exudate forms over the ulcers in many cases. Involvement of the oral mucosa anterior to Waldeyer's ring occurs in less than 10% of these cases. HSV appears to be a significant cause of pharyngotonsillitis in young adults who are from the higher socio-economic groups with previously negative test findings for

HSV antibodies. Most of these infections are HSV-I, but increasing proportions are HSV-2. The clinical presentation closely resembles pharyngitis secondary to streptococci or infectious mononucleosis, making the true frequency difficult to determine.

Recurrent infections may occur either at the site of primary inoculation or in adjacent areas of surface epithelium supplied by the involved ganglion. The most common site of recurrence for HSV-1 is the vermilion border and adjacent skin of the lips. This is known as **herpes labialis** ("cold sore" or "fever blister"). Prevalence studies suggest that from 15% to 45% of the United States population have a history of herpes labialis. In some patients, ultraviolet light or trauma can trigger recurrences. Prodromal signs and symptoms (e.g., pain, burning, itching, tingling, localized warmth, erythema of the involved epithelium) arise 6 to 24 hours before the lesions develop. Multiple small, erythematous papules develop and form clusters of fluid-filled vesicles. The vesicles rupture; crust within 2 days. Healing usually occurs within 7 to 10 days. Mechanical rupture of intact vesicles and the release of the virus-filled fluid may result in the spreading oft lesions on lips previously cracked from sun expos. Recurrences are observed less commonly on the skin of the nose, chin, or cheek.

Recurrences also can affect the oral mucosa. In the immunocompetent patient, involvement is limited almost always to keratinized mucosa that is bound to bone (attached gingiva and hard palate). These sites exhibit subtle changes, and the symptoms are intense. The lesions begin as 1 - to 3-mm vesicles that rapidly collapse to form a cluster of erythematous maccules that may coalesce or slightly enlarge. The damaged epithelium is lost, and a central yellowish area of ulceration develops. Healing takes place within 7 to 10 days.

Less common presentations of HSV-1 do occur. Infection of the thumbs or fingers is known as herpetic whit-r (herpetic paronychia), which may occur as a result self-inoculation in children with orofacial herpes. Before the uniform use of gloves, medical and dental personnel could infect their digits from contact with infected patients, and they were the most likely group affected by this form of HSV-I infection. Recurrences on the digits are not unusual and may result in paresthesia and permanent scarring.

Primary cutaneous herpetic infections can also arise in areas of previous epithelial damage. Parents kissing areas of dermatologic injury in children represent one vector. Wrestlers and rugby players also may contaminate areas of abrasion, a lesion called herpes gladiatorum or scrumpox. Ocular involvement may occur in children, often resulting from self-inoculation. Patients with diffuse chronic skin diseases, such as eczema, pemphigus, and Darier's disease, may develop diffuse life-threatening HSV infection, known as eczema herpeticum (Kaposi's varicelliform eruption). Newborns may become infected after delivery through a birth canal contaminated with HSV, usually HSV-2. Without treatment, there is greater than a 50% mortality rate.

HSV recurrence in immunocompromised hosts can be significant. Without proper immune function, recurrent herpes can persist and spread until the infection is treated with antiviral drugs, until immune status returns, or until the patient dies. On the skin, the lesions continue to enlarge peripherally, with the formation of an increasing zone of superficial cutaneous erosion. Oral mucosa also can be affected and usually is present in conjunction with herpes labialis. Although most oral mucosal involvement begins on the bound mucosa, it often is not confined to these areas. The involved sites begin as areas of necrotic epithelium, which is brownish and raised above the surface of the adjacent intact epithelium. Typically these areas are much larger than the usual pinhead lesions found in immunocompetent patients. With time, the area of involvement spreads laterally. The enlarging lesion is a zone of superficial necrosis or erosion, often with a distinctive circinate, raised, yellow border. This border represents the advancing margin of active viral destruction. Microscopic demonstration of HSV infection in a chronic ulceration on the movable oral mucosa is ominous, and all such patients should be evaluated thoroughly for possible immune dysfunction or underlying occult disease processes.

One group of investigators has described a pattern of chronic herpes that occurs on the dorsal surface of the tongue and appears as a deep midline fissure that typically exhibits multiple peripheral branches. This pattern has been nicknamed "geometric glossitis" and usually is symptomatic with areas of erosion in the depth of the fissures. However, the investigators used only culture for diagnosis. Because of the high prevalence of asymptomatic shedding of HSV in immunocompromised patients, viral culture is inadequate for diagnosis of intraoral lesions. Although the association between herpes simplex and

geometric glossitis needs to be confirmed through cytologic or histopathologic techniques, clinicians should investigate the possibility of HSV infection in immunocompromised patients with symptomatic lingual fissures.

Although a yellow curvilinear border often is present in many chronic herpetic ulcerations noted in immunocompromised patients, this distinctive feature might be missing. Several authors have reported persistent oral ulcerations in patients with acquired immunodeficiency syndrome (AIDS) that lack the distinctive periphery, often are nonspecific clinically, and may mimic aphthous ulcerations, necrotizing stomatitis, or ulcerative periodontal disease. Biopsy of persistent ulcerations in patients with AIDS is mandatory and may reveal any one of a number of infectious or neoplastic processes. These ulcers may reveal histopathologic evidence of her-pesvirus, often combined with diagnostic features of CMV (HHV-5) co-infection.

Histopathologic Features

The virus exerts its main effects on the epithelial cells. Infected epithelial cells exhibit acantholysis, nuclear clearing, and nuclear enlargement, which have been termed ballooning degeneration. The acantholytic epithelial cells are termed Tzanck cells. Nucleolar fragmentation occurs with a condensation of chromatin around the periphery of the nucleus. Multinucleated, infected epithelial cells are formed when fusion occurs between adjacent cells. Intercellular edema develops and leads to the formation of an intraepithelial vesicle. Mucosal vesicles rupture rapidly; those on the skin persist and develop secondary infiltration by inflammatory cells. Once they have ruptured, the mucosal lesions demonstrate a surface fibrinopurulent membrane. Often at the edge oft ulceration or mixed within the fibrinous exudate are the scattered Tzanck or multinucleated epithelial cells.

Diagnosis

With a thorough knowledge of the clinical presentations, the clinician can make a strong presumptive diagnosis HSV infection. On occasion, HSV infections can be confused with other diseases, and laboratory confirmatio is desirable. Viral isolation from tissue culture inoculated with the fluid of intact vesicles is the most definitive diagnostic procedure. The problem with this technique in primary infections is that up to 2 weeks can be required for a definitive result. Clinical tests for HSV antigens nucleic acids in specimens of active lesions also are available. Serologic tests for HSV antibodies are positive 4 to 8 days after the initial exposure. These antibody titers are useful in documenting past exposure and are us primarily in epidemiologic studies.

Intact vesicles are rare intraorally. Therefore, using intraoral viral culture as the sole means of diagnostic confirmation of HSV infection is inappropriate. It has been shown that asymptomatic oral HSV she occurs in up to 9% of the general population. During periods of mental or physical stress, asymptomatic viral shedding rises to approximately one third of those previously exposed to the virus. In immunocompromis patients, the prevalence rises to 38%; this percentage is low and most likely would double if the investigation were restricted to those previously exposed to the virus. Therefore, culture of lesions contaminated with saliva hat might contain coincidentally released HSV is meaningless unless supplemented by additional diagnostic procedures.

Two of the most commonly used diagnostic procedures the cytologic smear and tissue biopsy, with cytologic study being the least invasive and most cost-effective. The virus produces distinctive histologic alterations within the infected epithelium. Only VZV produces similar changes, but these two infections usually can be differentiated on a clinical basis. Fluorescent monoclonal antibody typing can be performed on the smears or on infected cells obtained from tissue culture.

If diagnostic features of herpesvirus are discovered in a biopsy of a persistent ulceration in an immunocompromised patient, immunocytochemical studies for CMV also should be performed to rule out co-infection. The pathologic features of CMV can be missed easily, lilting in patients not receiving the most appropriate therapy.

Treatment and Prognosis

In the past, primary herpetic gingivostomatitis was treated best symptomatically; however, if the infection is nosed early, antiviral medications can have a significant. Patients should be instructed to

restrict t with active lesions to prevent the spread to other sites and people. As mentioned previously, autoinoculation the eyes can result in ocular involvement with the ability of recurrence. Repeated ocular reinfection can produce permanent damage and blindness. HSV is the leading infectious cause of blindness in the United States.

When acyclovir suspension is administered in a rinse I swallow technique during the first 3 symptomatic significant acceleration in clinical resolution is seen. Once therapy is initiated, development of new lesions ceases. In addition, the associated eating and drinking difficulties, pain, healing time, duration of fever, and viral shedding are shortened dramatically. In addition topical rinsing with 0.5% or 1.0% dyclonine hydrochloride dramatically, but temporarily, decreases the mucosal discomfort. Viscous lidocaine should be avoided in pediatric patients because of reports of lidocaine-induced seizures in children. Nonsteroidal antiinflammatory medications, such as ibuprofen, also help alleviate the discomfort. Use viral medications in capsule or tablet form is much less effective because of the increased time these formulations require to exert a significant effect.

Recurrent herpes labialis has been treated with everything from ether to voodoo; nothing has solved the problem. Some minor successes have been achieved with the current brands of antivirals. Acyclovir and the two newer related medications, valacyclovir and famciclovir, appear to demonstrate similar effectiveness against HSV. Although valacyclovir and famciclovir exhibit improved bioavailability and more convenient oral dosing schedules, acyclovir remains an effective option. Although research by different investigators of drug effectiveness has produced variable results, these antiviral medications appear capable of minimizing recurrences if administered prophylactically. If begun early in the prodrome, the antiviral medications may reduce the number of lesions and the length of time to crusting. Pain and the length of time to healing are not affected significantly if the medication is not initiated during the prodrome. If prophylactic therapy is initiated before a known trigger, a further reduction in severity of the recurrence often is seen.

Because most cases of recurrent herpes labialis are mild and infrequent, regular use of systemic antiviral medications can be justified rarely in immunocompetent individuals without severe involvement. In recent years, the emergence of acyclovir-resistant HSV has been seen with increasing frequency. Such resistance has arisen almost exclusively in immunocompromised patients receiving intermittent therapy, and the use of prophylactic therapy does not appear to be associated with emergence of resistant strains. In immunocompromised patients, the viral load tends to be high and replication is not suppressed completely by antiviral therapy, creating the environment for generating drug-resistant mutants. Although resistance is seen primarily in chronic therapy in immunocompromised patients, cavalier use of antiviral medications for mild cases of recurrent herpes infection is inappropriate.

Acyclovir ointment in polyethylene glycol has been of limited benefit for herpes labialis in immunocompetent patients, because its base is thought to prevent significant absorption. In contrast, penciclovir cream is supplied in a base that allows increased absorption through the vermilion border. Use of this formulation has been shown to result in a statistically significant, although clinically minimal, reduction in healing time and pain (duration decreased less than 1 day). Although the effects of this therapy were minimal in a large study group initiating therapy during the prodromal period, some patients experienced dramatic response, especially many with more severe involvement. It may be that the initiation of topical therapy during the prodrome is too late, and significant success may be possible only in patients who associate recurrences with a known trigger and are able to begin prophylactic treatment before the first symptoms appear.

Two recent additions to current topical therapies mandate further independent study. A heavily advertised over-the-counter formulation of 10% n-docosanol cream is available and has been reported in a limited number of evaluations to shorten mean healing time by approximately 3 days. Recently a formulation of "quan-tanary ammonium chlorides, dimethyl carbonal, and other chemicals" has been marketed through dentists and dermatologists for the treatment of herpes labialis. Until this treatment has been sufficiently scientifically tested and proven to be effective, its use cannot be recommended.

The pain associated with intraoral secondary herpes usually is not intense, and many patients do not require treatment. Some studies have shown chlorhexidine to exert antiviral effects in vivo and in vitro. In addition, acyclovir appears to function synergistically with chlorhexidine. Extensive clinical trials have not

been performed, but chlorhexidine alone or in combination with acyclovir suspension may be beneficial in patients who desire or require therapy of intraoral lesions.

Immunocompromised hosts with HSV infections often require intravenous antiviral medications to control the problem. Furthermore, severely immunosuppressed individuals, such as bone marrow transplant patients and those with AIDS, often need prophylactic doses of oral acyclovir, valacyclovir, or famciclovir. On occasion, viral resistance develops, resulting in the onset of significant herpetic lesions. Any herpes lesions that do not respond to appropriate therapy within 5 to 10 days most likely are the result of resistant strains. These resistant strains have been treated successfully with trisodium phosphonoformate hexahydrate (foscarnet), but this medication is reserved as a second-line therapy because of its significant side effects. In these cases, it appears that only the peripheral virus mutates, because future recurrences are once again sensitive to the first-line antivirals. Ulcerations that reveal co-infection with HSV and CMV respond well to ganciclovir, with foscarnet used in refractory cases.

Although a successful live-virus vaccine has been available for the closely related varicella virus for over 25 years, similar approaches against HSV have produced less satisfactory results. Significant research for a potential vaccine is ongoing and offers hope for the future.

VARICELLA (CHICKENPOX)

The varicella-zoster virus (VZV; HHV-3) is similar to herpes simplex virus (HSV) in many respects. Chicken pox represents the primary infection with the VZV; latency ensues, and recurrence is possible as herpes zoster, often after many decades. The virus is presumed to be spread through air droplets or direct contact with active lesions. Most cases of chickenpox arise between the ages of 5 and 9, with greater than 90% of the United States population being infected by 15 years of age. In contrast to infection with HSV, most cases are symptomatic. The incubation period is 10 to 21 days, with an average of 15 days.

Clinical Features

The symptomatic phase of VZV infection usually begins with malaise, pharyngitis, and rhinitis. In older children and adults, additional symptoms (e.g., headache, myalgia, nausea, anorexia, vomiting) occasionally are seen. This is followed by a characteristic, intensely pruritic exanthem. The rash begins on the face and trunk, followed by involvement of the extremities. Each lesion rapidly progresses through stages of erythema, vesicle, pustule, and hardened crust. The early vesicular stage is the classic presentation. The centrally located vesicle is surrounded by a zone of erythema and has been described as "a dewdrop on a rose petal." In contrast to herpes simplex, the lesions typically continue to erupt for 4 days; in some cases, the exanthem's arrival (may extend to 7 or more days. Old crusted lesions intermixed with newly formed and intact vesicles are commonplace. Affected individuals are contagious from 2 days before the exanthem until all the lesions crust. Fever usually is present during the active phase of the exanthem. The severity of the cutaneous involvement is variable members secondarily infected by the initial patient.

Oral lesions are fairly common and may precede the skin lesions. The palate and the buccal mucosa are involved most frequently. Occasionally, gingival lesions resemble those noted in primary HSV infections, but distinguishing between the two is not difficult because the lesions of varicella tend to be relatively painless. The lesions begin as 3- to 4-mm white opaque vesicles that rupture to form 1- to 3-mm ulcerations.

Complications can occur, with the need for hospitalization in children approximating 1 in 600 in the prevaccine era. Possible complications include Reye's syndrome, secondary skin infections, encephalitis, cerebellar jataxia, pneumonia, gastrointestinal disturbances (e.g., vomiting, diarrhea, and associated dehydration), and hematologic events (thrombocytopenia, pancytopenia, emolytic anemia, sickle cell crisis).

In childhood, the most frequent complications are secondary skin infections, followed by encephalitis and pneumonia. With enhanced public education and decreased use of aspirin in children, the prevalence of Reye's syndrome is decreasing. Although associated bacterial infections had decreased after the introduction of antibiotics, an increased prevalence of significant complications related to secondary infections caused by group A, β-hemoIytic streptococci was seen during the 1990s. These organisms have created life-threatening infections and areas of highly destructive necrotizing fasciitis.

The prevalence of complications in adults exceeds that noted in children. The risk of death between 15 to 19 years of age is 2.7/100,000 but rises to 25.2/100,000 in patients aged 30 to 49 years. The most common and serious complication is varicella pneumonitis, which features dry cough, tachypnea, dyspnea, hemoptysis, chest pain, and cyanosis. Encephalitis and clinically significant pneumonia are diagnosed in I in 375 affected adults older than 20 years of age. The central nervous system involvement typically produces ataxia but may result in headaches, drowsiness, convulsions, or coma.

Infection during pregnancy can produce congenital or neonatal chickenpox. Involvement early in the pregnancy can result in spontaneous abortion or congenital defects. Although complications can occur in newborns, the effects of maternal varicella infection appear minimal. A recent multicenter prospective study of live births associated with maternal varicella infection revealed only a 1.2% prevalence of embryopathy. However, infection of the mother close to delivery can result in a severe fetal infection caused by a lack of maternal antibodies.

Infection in immunocompromised patients also can be most severe. The cutaneous involvement typically is extensive and may be associated with high fever, hepatitis, pneumonitis, pancreatitis, gastrointestinal obstruction, and encephalitis. Before effective antiviral therapy, the mortality rate in immunocompromised individuals was approximately 7%. Secondary bacterial infections often complicate the process.

Histopathologic Features

The cytologic alterations are virtually identical to those described for HSV. The virus causes acantholysis, with formation of numerous free-floating Tzanck cells, which exhibit nuclear margination of chromatin and occasional multinucleation.

Diagnosis

The diagnosis of chickenpox usually can be made from a history of exposure to VZV within the last 3 weeks and the presence of the typical exanthem. Confirmation can be obtained through a demonstration of viral cytopathologic effects present within the epithelial cells harvested from the vesicular fluid. These cytologic changes are identical to those found in herpes simplex, and further confirmation sometimes is desired. Viral isolation in cell culture or rapid diagnosis from fluorescein-conjugated VZV monoclonal antibodies can be performed. Finally, serum samples can be obtained during the acute stage and 14 to 28 days later. The later sample should demonstrate a significant (fourfold) increase in antibody tilers to VZV.

Treatment and Prognosis

Before the current antiviral medications became avail able, the treatment of varicella primarily was symptom matic. Warm baths with soap or baking soda, application of calamine lotion, and systemic diphenhydramine still are used to relieve pruritus. VZV has a lipid envelope that is destroyed rapidly by soap and other detergents. Lotions with diphenhydramine are not recommended because of reports of toxicity secondary to percutaneous absorption of the medication. Antipyretics other than aspirin should be given to reduce fever. I

Use of peroral antiviral medications such as acyclovir, valacyclovir, and famciclovir has been shown to reduce the duration and severity of the infection if it is administered within the first 24 hours of the rash. Routine use of these antiviral medications is not recommended in immunocompetent children with uncomplicated chicken pox. Typically, such therapy is reserved for patients at risk for more severe disease, such as those over 13 years of age and individuals who contract the disease from a family member. Intravenous formulations are used in immunosuppressed patients or those exhibiting a progressive, severe infection. Treatment with one of the available antiviral medications does not alter the antibody response to VZV or reduce immunity later in life.

In immunocompromised patients who become exposed to VZV, varicella-zoster immune globulin (VZIG) can be given to modify the clinical manifestations of the infection. VZIG is available commercially and prevents severe varicella infections in immunocompromised patients. In addition, infants born of mothers exhibiting a varicella rash of less than 4-days duration demonstrate a risk of death that exceeds 30%. Use of VZIG in these infants is associated with a markedly improved prognosis.

A live attenuated VZV vaccine has been available since 1974 and has been used extensively outside the United States, especially in Japan. The vaccine is 98% effective, with a 1 % prevalence of rash and fever. In the United States, routine vaccination of children is recommended between 12 and 18 months of age. Typically, the vaccine is given at the same time as the measles-mumps-rubella (MMR) vaccine (but in a separate syringe and in a different injection site). Patients older than 18 months who lack a reliable history of varicella also are recommended for vaccination but should receive a systemic review for several contraindications before vaccination.

During the first year after vaccination, the efficacy appears to be 100% but drops to 95% after 7 years. When breakthrough infections do occur, they usually are very mild. Because of continued exposure to wild virus, previously vaccinated patients have not required boosters to maintain immunity. As the wild virus fades, booster vaccines may be required to maintain lifelong immunity. Extensive follow-up of vaccinated groups is ongoing; if antibody levels wane with time, booster immunization will be recommended. Each year slightly fewer than deaths are reported secondary to VZV in the United States. However, the number of deaths most likely will decrease a result of the use of antiviral medications and vaccine. It should be remembered that the vaccine is a live virus that can be spread to individuals in close contact. Vaccine recipients who develop a rash should avoid contact with those at risk, such as immunocompromised or pregnant individuals.

HERPES ZOSTER (SHINGLES)

After the initial infection with VZV (chickenpox), the virus is transported up the sensory nerves and presumably establishes latency in the dorsal spinal ganglia. Clinically evident herpes zoster occurs after reactivation of the virus, with the involvement of the distribution of the affected sensory nerve. Zoster occurs during the lifetime of 10% to 20% of individuals, and the prevalence of attacks increases with age. With the increasing average age of the population, an increased prevalence of herpes zoster is expected. Unlike herpes simplex virus (HSV), single rather than multiple recurrences are the rule. Immunosuppression, treatment with cytotoxic drug radiation, presence of malignancies, old age, alcohol abuse, and dental manipulation are predisposing factors for reactivation.

Clinical Features

The clinical features of herpes zoster can be grouped into three phases: prodrome, acute, and chronic. During initial viral replication, active ganglionitis develops with resultant neuronal necrosis and severe neuralgia. This inflammatory reaction is responsible for the prodromal symptoms of intense pain that precedes the rash in more than 90% of the cases. As the virus travels down the nerve, the pain intensifies and has been described as burning, tingling, itching, boring, prickly, or knifelike. The pain develops in the area of epithelium innervated by the affected sensory nerve (dermatome). Typically, one dermatome is affected, but involvement of two or more can occur. This prodromal pain, which may be accompanied by fever, malaise, and headache, normally is present l to 4 days before the development of the cutaneous or mucosal lesions. During this period (before the exanthema) the pain may masquerade as sensitive teeth, otitis media, migraine headache, myocardial infarction, or appendicitis, depending on which dermatome is affected.

Approximately 10% of affected individuals will exhibit no prodromal pain. Conversely, on occasion there may be recurrence in the absence of vesiculation of the skin or mucosa. This pattern is called zoster sine herpete (zoster without rash), and affected patients have severe pain of abrupt onset and hyperesthesia over a specific dermatome. Fever, headache, myalgia, and lymphadenopathy may or may not accompany the recurrence.

The acute phase begins as the involved skin develops clusters of vesicles set on an erythematous base. Within 3 to 4 days, the vesicles become pustular and ulcerate, with crusts developing after 7 to 10 days. The lesions tend to follow the path of the affected nerve and terminate at the midline. The exanthem typically resolves within 2 to 3 weeks in otherwise healthy individuals. Upon healing, scarring with hypopigmention or hyperpigmention is not unusual.

Oral lesions occur with trigeminal nerve involvement and may be present on the movable or bound mucosa. The lesions often extend to the midline and frequently are present in conjunction with involvement of the skin overlying the affected quadrant. Like varicella, the individual lesions present as 1- to 4-mm

white opaque vesicles, which rupture to form shallow ulcerations. Involvement of the maxilla may be associated with devi-talization of the teeth in the affected area. In addition, several reports have documented significant bone necrosis with loss of teeth in areas involved with herpes zoster.

Ocular involvement is not unusual and can be the source of significant morbidity, including permanent blindness. The ocular manifestations are highly variable and may arise from direct viral-mediated epithelial damage, neuropathy, immune-mediated damage, or secondary vasculopathy. If the tip of the nose is involved, this is a sign that the nasociliary branch of the fifth cranial nerve is involved, suggesting the potential for ocular infection. In these cases, referral to an ophthalmologist is mandatory.

Facial paralysis has been seen in association with herpes zoster of the face or external auditory canal. Ramsay Hunt syndrome is the combination of cutaneous lesions of the external auditory canal and involvement of the ipsilateral facial and auditory nerves. The syndrome causes facial paralysis, hearing deficits, vertigo, and a number of other auditory and vestibular symptoms.

Many patients do not progress to the chronic phase. This occurs when the neuralgia-associated pain persists longer than 3 months after the initial presentation of the acute rash. This is termed postherpetic neuralgia and occurs in up to 15% of affected patients and at least 50% of patients older than 60 years of age. The pain is described as burning, throbbing, aching, itching, or stabbing, often with flares caused by light stroking of the area or from contact with adjacent clothing. Most of these neuralgias resolve within 1 year, with one half of the patients experiencing resolution after 2 months. Rare cases may last up to 20 years, and patients have been known to commit suicide as a result of the severe, lancinating quality of the pain.

Histopathologic Features

The active vesicles of herpes zoster are identical microscopically to those seen in the primary infection, varicella. For more information, refer to the previous portions of the chapter on the histopathologic presentation of varicella and herpes simplex.

Diagnosis

The diagnosis of herpes zoster often can be made from the clinical presentation, but other procedures may be necessary in atypical cases. Viral culture can confirm the clinical impression but takes at least 24 hours. Cytologic smears demonstrate viral cytopathologic effects, as seen in varicella and HSV. In most cases, the clinical presentation allows the clinician to differentiate zoster from HSV, but cases of zosteriform recurrent HSV infection, although uncommon, do exist. A rapid diagnosis can be obtained through the use of direct staining of cytologic smears with fluorescent monoclonal antibodies for VZV. This technique gives positive results in almost 80% of the cases. Molecular techniques such as dot-blot hybridization and polymerase chain reaction (PCR) also can be used to detect VZV.

Treatment and Prognosis

Before the development of the current antiviral medications, therapy for herpes zoster was directed toward supportive and symptomatic measures. Fever should be treated with antipyretics that do not contain aspirin. Antipruritics, such as diphenhydramine, can be administered to decrease itching. Skin lesions should be kept dry and clean to prevent secondary infection; antibiotics may be administered to treat such secondary infections. Early therapy with appropriate antiviral medications such as acyclovir, valacyclovir, and famciclovir has been found to accelerate healing of the cutaneous and mucosal lesions, reduce the duration of the acute pain, and decrease the duration of postherpetic neuralgia. These medications are most effective if initiated within 72 hours after development of the first vesicle. Although none of these medications has been proven to reduce the preva- lence of postherpetic pain, the newer formulations, famciclovir and valacyclovir, have more convenient dosing regimens and greater bioavailability. Although several investigations have suggested the newer drugs are more effective than acyclovir in minimizing the acute phase and reducing the duration of postherpetic neuralgia, such differences have not been demonstrated conclusively.

Once the skin lesions have healed, the neuralgia may become the worst aspect of the disease and often is the most difficult to resolve successfully. This intense pain has been treated with variable results by a variety of methods including analgesics, narcotics, tricyclic antidepressants, anticonvulsants,

percutaneous electric nerve stimulation, biofeedback, nerve blocks, and topical anesthetics.

One topical treatment, capsaicin, has had significant success, with almost 80% of patients experiencing some pain relief; however, the medication's effect often does not occur until 2 weeks or more of therapy. Capsaicin is derived from red peppers and is not recommended for placement on mucosa or open cutaneous lesions. Capsaicin has been associated with significant burning, stinging, and redness in 40% to 70% of patients, with up to 30% discontinuing therapy because of this side effect. After use, patients must be warned to wash their hands and avoid contact with mucosal surfaces.

Corticosteroid therapy has been used in the hope it might decrease the neural inflammation and associated chronic pain. Although conflicting research has been published, studies have shown no long-term benefit when corticosteroids are added to an acyclovir regime. In addition, an increased prevalence of side effects was noted in groups treated with corticosteroids.

Preliminary studies evaluating a live attenuated varicella vaccine have shown an improved immune response to the virus in elderly patients. Larger studies may lead to the use of this vaccine in an attempt to decrease the frequency of disease in this vulnerable population.

INFECTIOUS MONONUCLEOSIS (MONO; GLANDULAR FEVER; "KISSING DISEASE")

Infectious mononucleosis is a symptomatic disease resulting from exposure to Epstein-Barr virus (EBV, HHV-4). The infection usually occurs by intimate contact. Intrafamilial spread is common, and once a person is exposed, EBV remains in the host for life. Children usually become infected through contaminated saliva on fingers, toys, or other objects. Adults usually contract the virus through direct salivary transfer, such as shared straws or kissing, hence, the nickname “kissing disease”.

Exposure during childhood usually is asymptomatic, and most symptomatic infections arise in young adults. In deveeloping nations, exposure usually occurs by age 3 and in universal by adolescence. In the United States, introduction to the virus often is delayed, with close to 50% of college students lacking previous exposure. These unexposed adults become infected at a rate of 10% to 15% per year while in college. Infection in adulthood is associated with *a* higher risk (i.e., 30% to 50%) for symptomatic disease.

Besides infectious mononucleosis, EBV has been demonstrated in the lesions of oral hairy leukoplakia (OHL) and has been associated with a number of lymphoproliferative disorders, a variety of lymphomas (most notably African Burkitt's lymphoma), nasopharyngeal carcinoma, some gastric carcinomas, and occasional smooth muscle tumors. However, direct proof of a cause-and-effect relationship is lacking.

Clinical Features

Most EBV infections in children are asymptomatic. In children younger than 4 years of age with symptoms, most have fever, lymphadenopathy, pharyngitis, hepato-splenomegaly, and rhinitis or cough. Children older than 4 years of age are affected similarly but exhibit a much lower prevalence of hepatosplenomegaly, rhinitis, and cough.

Most young adults experience fever, lymphadenopathy, pharyngitis, and tonsillitis. Hepatosplenomegaly and rash are seen less frequently. In adults older than 40 years of age, fever and pharyngitis are the predominant findings, with less than 30% demonstrating lymphadenopathy. Less frequent signs and symptoms in this groupup include hepatosplenomegaly, rash, and rhinitis or cough. Possible significant complications include splenic rupture, thrombocytopenia, autoimmune hemolytic anemia, and neurologic problems with seizures. These complications are uncommon at any age but more frequently develop in children.

In classic infectious mononucleosis in a young adult, prodromal fatigue, malaise, and anorexia occur up to 2 weeks before the development of pyrexia. The temperature may reach 104° F and lasts from 2 to 14 days. Prominent lymphadenopathy is noted in more than 90% of the cases and typically appears as enlarged, symmetric, and tender nodes, frequently with involvement of the posterior and anterior cervical chains. Enlargement of parotid lymphoid tissue rarely has been reported and can be associated with facial nerve palsy. More than 80% of affected young adults have oropharyngeal tonsillar enlargement, sometimes with diffuse surface exudates and secondary tonsillar abscesses. In rare instances, this enlargement may increase to the point of airway obstruction and even death.

Oral lesions other than lymphoid enlargement also may be seen. Petechiae on the hard or soft

palate are present in about 25% of patients. The petechiae are transient and usually disappear within 24 to 48 hours. Necrotizing ulcerative gingivitis (NUG) also is fairly common. NUG-like pericoronitis and necrotizing ulcerative mucositis occur less frequently. Cases of NUG that are refractory to normal therapy should be evaluated to rule out the possibility of EBV.

A controversial symptom complex called chronic fatigue syndrome has been described, and several investigators have tried to associate EBV with this problem. Patients complain of rather nonspecific symptoms of chronic fatigue, fever, pharyngitis, myalgias, headaches, arthralgias, paresthesias, depression, and cognitive defects. These patients often demonstrate elevations in EBV antibody titers, but this finding alone is insufficient to prove a definite cause-and-effect relationship. Several studies have cast serious doubt on a relationship between EBV and the chronic fatigue syndrome.

Diagnosis

The diagnosis of EBV is suggested by the clinical presentation and should be confirmed through laboratory procedures. The white blood cell (WBC) count is increased, with the differential count showing relative lymphocytosis that can become as high as 70% to 90% during the second week. Atypical lymphocytes usually are present in the peripheral blood. The classic serologic finding in EBV is the presence of the Paul-Bunnell heterophil antibody; a rapid test for these antibodies is available and inexpensive. More than 90% of infected young adults have positive findings for the heterophil antibody, but infected children younger than age 4 frequently have negative results. Indirect immunofluorescent testing to detect EBV-specific antibodies should be used in those suspected of having an EBV infection but whose findings were negative on the Paul-Bunnell test. Enzyme-linked immunosorbent assays (ELISA) and recombinant DNA-derived antigens may soon replace the indirect immunofluorescent test.

Treatment and Prognosis

In most cases, infectious mononucleosis resolves within 4 to 6 weeks. Nonaspirin-containing antipyretics and nonsteroidal antiinflammatory medications can be used to minimize the most common symptoms. Infrequent complications include splenic rupture, EBV-related hepatitis, and Bell's palsy. Patients with significant enlargement of the spleen should avoid contact sports to prevent the rare possibility of splenic rupture. On occasion, the fatigue may become chronic. In immunocompromised patients, a polyclonal B-lymphocyte proliferation may occur and possibly lead to death.

The tonsillar involvement may, on occasion, resemble streptococcal pharyngitis or tonsillitis. However, treatment with ampicillin and penicillin should be avoided because the use of these antibiotics in infectious mononucleosis has been associated with a higher than normal prevalence of allergic morbilliform skin rashes.

Corticosteroid use is the recommended therapy in many textbooks. Such drugs, however, should not be used indiscriminately because the person's immune response appears to be the most important factor in fighting the infection and preventing a potentially fatal polyclonal B-lymphocyte proliferation. In addition, an increased prevalence of encephalitis and myocarditis has been noted in patients who have infectious mononucleosis and are treated with steroids. Corticosteroid use produces a shortened duration of fever and shrinkage of enlarged lymphoid tissues, but its use should be restricted to life-threatening cases (such as those with upper-airway obstruction because of massive lymphadenopathy).

CYTOMEGALOVIRUS

Cytomegalovirus (CMV, HHV-5) is similar to the other human herpes viruses (i.e., after the initial infection, latency is established and reactivation is possible under conditions favorable to the virus). CMV can reside latently in salivary gland cells, endothelium, macrophages, and lymphocytes. Most clinically evident disease is found in neonates or in immunosuppressed adults. In infants, the virus is contracted through the placenta, during delivery, or during breast-feeding. The next peak of transmission occurs during adolescence, predominantly from the exchange of bodily fluids as this group begins sexual activity. Transmission also has been documented from blood transfusion and organ transplantation. The prevalence of neonatal CMV infection varies from 0.5% to 2.5%. By the age of 30, almost 40% of the population is infected; by age 60, 80% to 100% are infected. Screening of healthy middle-aged adult blood donors reveals that approximately 50% have been exposed to CMV.

Clinical Features

At any age, almost 90% of CMV infections are asymptomatic. In clinically evident neonatal infection, the infant appears ill within a few days. Typical features include hepatosplenomegaly, extramedullary cutaneous erythropoiesis, and thrombocytopenia (often with associated petechial hemorrhages). Significant encephalitis frequently leads to severe mental and motor retardation.

Acute adult infection exhibits a clinical pattern that is similar to that of infectious mononucleosis. Most patients have fever, malaise, myalgia, abnormal liver function tests, and atypical peripheral lymphocytes. In contrast to patients with infectious mononucleosis, only about one third of patients with CMV demonstrate pharyngitis and lymphadenopathy. Rarely, immunocompetent patients may show signs of an acute sialadenitis that diffusely involves all of the major and minor salivary glands. In such cases, xerostomia often is noted and the affected: glands are painful. Involvement of the major glands usually results in clinically obvious enlargements of the parotid and submandibular glands.

Evident CMV involvement is not unusual in immunocompromised transplant patients. In some cases a temporary mild fever is the only evidence; in others, the infection becomes aggressive and is characterized by significant hepatitis, leukopenia, pneumonitis, and, more rarely, a progressive wasting syndrome.

CMV disease is common in patients with AIDS. CMV chorioretinitis affects almost one third of patients with AIDS and tends to progress rapidly, often resulting in blindness. Bloody diarrhea from CMV colitis is fairly common but may respond to appropriate antiviral medications.

Although oral lesions from CMV infection have been documented in a number of imunosuppressive conditions, reports of oral involvement by CMV have been increasing since the advent of the AIDS epidemic. Most affected patients have chronic mucosal ulcerations, and CMV changes are found on biopsy. Occasionally, chronic oral ulcerations in immunocompromised patients will demonstrate co-infection (usually CMV combined with HSV).

Neonatal CMV also can produce developmental tooth defects. Examination of 118 people with a history of neonatal CMV infection revealed tooth defects in 40% of those with symptomatic infections and slightly more than 5% of those with asymptomatic infections. The teeth exhibited diffuse enamel hypoplasia, significant attrition, areas of enamel hypomaturation, and yellow coloration from the underlying dentin.

Histopathologic Features

Biopsy specimens of intraoral CMV lesions usually demonstrate changes within the vascular endothelial cells. Scattered infected cells are extremely swollen, showing both intracytoplasmic and intranuclear inclusions and prominent nucleoli. This enlarged cell has been called an "owl eye" cell. Gomori's methenamine silver and periodic acid-Schiff (PAS) stains demonstrate the aplasmic inclusions but not the intranuclear changes. Salivary ductal epithelium also may be affected and form “owl eye” cells.

Diagnosis

The diagnosis of CMV is made by considering a combination of the clinical features and by conducting other aminations. Biopsy material can demonstrate cellular changes that suggest infection. Because effective therapies exist for CMV infections in immunocompromised patients, biopsies are recommended for chronic ulcerations that are not responsive to conservative therapy. More specific verification can be made by electron microscopy, detection of viral antigens by immunohistochemistry, *in situ* hybridization, polymerase chain reaction, demonstration of rising viral antibody liters, or viral culture.

In immunocompromised patients with chronic ulcerations, the typical "owl eye" cells may be few and difficult to discover upon routine light microscopy. When biopsy is performed upon a chronic oral ulceration in these patients, *in situ* hybridization or immunohistochemical evaluation for CMV should be performed, even in the absence of "owl eye" cells. In addition, close examination to rule out co-infection by HSV also should be performed.

Treatment and Prognosis

Although most CMV infections resolve spontaneously, therapy often is required in the

immunosuppressed patient. Ganciclovir has resolved clinical symptoms in more than 75 % of treated immunocompromised patients. However, the medication must be continued to prevent a relapse if the immune dysfunction persists. In patients with oral ulcerations co-infected with CMV and HSV, intravenous ganciclovir will produce resolution in most instances. The development of resistance to ganciclovir has been reported, but successful resolution of these resistant infections has been achieved with foscarnet.

ENTEROVIRUSES

The genus enterovirus encompasses the poliovirus, coxsackievirus A and B, echovirus, and enterovirus groups. Of these, more than 30 exist that can result in symptomatic infections associated with rashes. Few are distinctive enough clinically to allow differentiation from one another. Most are asymptomatic or subclinical. These infections may arise at any age, but most occur in infants or young children. Neonatal cases also have been reported. Only herpangina, hand-foot-and-mouth disease, and acute lymphonodular pharyngitis deserve discussion. These three clinical patterns are related closely and should not be considered entirely separate infections. In reports of epidemics in which a large number of patients acquire the same strain of the virus, the clinical presentations often are variable and include both herpangina and hand-foot-and-mouth disease.

Herpangina usually is produced by coxsackievirus A 1 to 6, 8, 10, or 22. However, it also may represent infection by coxsackievirus A 7, 9, or 16; coxsackievirus B 2 to 6; echovirus 9, 16, or I 7; or enterovirus 71. Hand-foot-and-mouth disease usually is caused by coxsackievirus A 16 but may also arise from coxsackievirus A 5, 9, or 10; echovirus 11; or enterovirus 71. Acute lymphonodular pharyngitis is less recognized, and coxsackievirus A10 has been found in the few reported cases. The incubation period for these viruses is 4 to 7 days.

Most cases arise in the summer or early fall in non-tropical areas, with crowding and poor hygiene aiding their spread. The fecal-oral route is considered the major path of transmission, and frequent hand washing is emphasized in an attempt to diminish spread during epidemics. During the acute phase, the virus also can be transmitted through saliva or respiratory droplets. Infection confers immunity against reinfection to that one strain. In spite of the developed immunity, people may become infected numerous times with different enterovirus types over several years while still remaining susceptible to other different strains.

Clinical Features

In many countries, epidemics occur every 2 to 3 years and primarily affect children aged 1 to 4 years. The timing of the epidemics appears to be correlated to the accumulation of a new population of susceptible young children. In all three clinical patterns, the severity and significant complications are variable and appear associated with the particular strain that is responsible. In general, most strains produce a self-limiting disease that requires no therapy, but occasional strains can produce epidemics with an increased number of significant complications and occasional mortalities. Systemic complications include pneumonia, pulmonary edema and hemorrhage, acute flaccid paralysis, encephalitis, meningitis, and carditis.

In 1998, a massive epidemic spread over Taiwan (population 21,178>000), and it is estimated that approximately 1.5 million patients developed clinical evidence of the infection. A group of sentinel physicians (8.7% of primary physicians) documented 129,106 infected patients. Of these patients, the vast majority were infected with enterovirus 71; a much lesser number were infected with one of a number of coxsackieviruses (predominantly A 16). When patients infected with the same strain were examined, clinical patterns diagnostic of both herpangina and hand-foot-and-mouth disease were detected. In this epidemic, more than 75% had symptoms of hand-foot-and-mouth disease, but it is clear these two clinical patterns represent variations of the same disorder.

Herpangina. Herpangina begins with an acute onset of significant sore throat, dysphagia, and fever, occasionally accompanied by cough, rhinorrhea, anorexia, vomiting, diarrhea, myalgia, and headache. Most cases, however, are mild or subclinical. A small number of oral] lesions, usually two to six, develop in the posterior areas of the mouth, usually the soft palate or tonsillar pillars. The affected areas begin as red macules, which form fragile vesicles that rapidly ulcerate. The ulcerations average 2 to 4 mm in

diameter. The systemic symptoms resolve within a few days; as would be expected, the ulcerations usually take 7 to 10 days to heal.

Hand-foot-and-mouth disease. Hand-foot-and-mouth disease is the most well-known enterovirus infection. Like herpangina, the skin rash and oral lesions typically are associated with flulike symptoms (e.g., sore throat, dysphagia, fever), occasionally accompanied by cough, rhinorrhea, anorexia, vomiting, diarrhea, myalgia, and headache.

The name fairly well describes the location of the lesions. Oral lesions and those on the hands almost always are present; involvement of other cutaneous sites is more variable. The oral lesions arise without prodromal symptoms and precede the development of the j cutaneous lesions. Sore throat and mild fever are present. The cutaneous lesions range from a few to dozens and primarily affect the borders of the palms and soles and the ventral surfaces and sides of the fingers and toes. Rarely other sites, especially the buttocks, external genitals, and legs, may be involved. The individual cutaneous lesions begin as erythematous macules I that develop central vesicles and heal without crusting.

The oral lesions resemble those of herpangina bull may be more numerous and are not confined to the posterior areas of the mouth. The number of lesions ranges from 1 to 30. The buccal mucosa, labial mucosa, and tongue are the most common sites to be affected, but any area of the oral mucosa may be involved, The individual vesicular lesions rapidly ulcerate and are typically 2 to 7 mm in diameter but may be larger than 1 cm. Most of these ulcerations resolve within 1 week.

Acute lymphonodular pharyngitis. Acute lympho-nodular pharyngitis is characterized by sore throat, fever, and mild headache, which may last from 4 to 14 days. Low numbers (one to five) of yellow to dark pink nodules develop on the soft palate or tonsillar pillars. The nodules represent hyperplastic lymphoid aggregates and resolve within 10 days without vesiculation or ulceration. Few cases have been described, and whether this represents a distinct clinical entity is as yet unresolved. The possibility that the sore throat and palatal lymphoid hyperplasia represent features of herpangina or some other infection cannot be excluded without further documentation of additional cases.

Histopathologic Features

In patients with herpangina and hand-foot-and-mouth disease, the areas of affected epithelium exhibit intracellular and intercellular edema, which leads to extensive spongiosis and the formation of an intraepithelial vesicle. The vesicle enlarges and ruptures through the epithelial basal cell layer, with the resultant formation of a subepithelial vesicle. Epithelial necrosis and ulceration soon follow. Inclusion bodies and multinucleated epithelial cells are absent.

Diagnosis

The diagnoses of herpangina, hand-foot-and-mouth disease, and acute lymphonodular pharyngitis usually are made from the distinctive clinical manifestations. In patients with atypical presentations, laboratory confirmation appears prudent. Viral isolation from culture can be performed, and analysis of stool specimens is the best technique in patients with only mucosal lesions. Throat culture findings tend to be positive predominantly during the early acute stage. The culture of cutaneous lesions is best for the diagnosis of hand-foot-and-mouth disease. A serologic demonstration of rising enteroviral antibody liters between the acute and convalescent stages can be used to confirm the diagnosis in questionable cases.

Treatment and Prognosis

In most instances, the infection is self-limiting and without significant complications. Therapy for patients with an enterovirus infection is directed toward symptomatic relief. Nonaspirin antipyretics and topical anesthetics, such as dyclonine hydrochloride, often are beneficial.

Occasionally, certain strains produce infections with a more aggressive clinical course. During the 1998 epidemic in Taiwan, a large group of physicians reported 405 patients with severe disease and 78 deaths. Patients with more significant complications demonstrated higher temperature (>39° C), fever for longer than 3 days, more serious vomiting, and greater lethargy. When these findings are

present, the physician must monitor the patient more closely for the development of more serious complications.

RUBEOLA (MEASLES)

Rubeola is an infection produced by a paramyxovirus and exhibits a variable prevalence that is correlated to the degree of vaccine use. Measles vaccine has been in wide use in the United States since 1963 and is 95% effective, resulting in a 98% reduction in the prevalence of this infection. Before 1963, virtually all children acquired measles, but the vaccine produced a continued and significant decline until the late 1980s. From 1989 to 1991, a major resurgence occurred with an increasing proportion of cases among unvaccinated preschool-aged children, particularly minority residents of densely populated urban areas. In addition, a smaller number of cases appeared to be associated with vaccine failure.

Clinical Features

Most cases of measles arise in the spring and are spread through respiratory droplets. Affected individuals are infectious from 2 days before becoming symptomatic until 4 days after appearance of the rash. After an incubation period of 10 to 12 days, the infection begins with prodromal symptoms of fever, malaise, coryza (runny nose), conjunctivitis, and cough. The well-known exanthematous rash follows after a few days and lasts from 4 to 7 days. The face is involved first, with eventual j downward spread to the trunk and extremities. Ultimately, a diffuse erythematous maculopapular eruption j is formed. The rash clears in a similar downward progression and is replaced by a brown pigmentary staining.

Common complications in young children are otitis, pneumonia, persistent bronchitis, and diarrhea. Encephalitis develops in approximately 1 in 1000 cases, often resulting in death or permanent brain damage and mental retardation. In about 1 in 100,000 cases, a delay complication termed subacute sclerosing panencephalitis (SSPE) arises as late as 11 years after the initial infection. This degenerative disorder of the CNS leads to personality changes, seizures, coma, and death. Widespread vaccine use has virtually eliminated SSPE in developed nations. In the United States, 1 to 2 deaths occur for every 1000 reported cases of measles. In developing countries, the infection often is more severe, and the case-to-fatality rate can be as high as 25%. The most common causes of death are pneumonia and acute encephalitis.

Measles in immunocompromised patients can serious, with a high risk of complications and death. Most of these patients exhibit either an atypical rash or no exanthem. Pneumonitis is the primary complication. The fatality rate of measles in patients with a malignancy is greater than 50%; AIDS-associated measles results in death of more than one third of the affected patients.

Lesions, known as Koplik's spots, are the most distinctive oral manifestation of measles and develop early in the course of the infection. Multiple areas of mucosal erythema are visible on the buccal and labial mucosa or less often on the soft palate; within these areas, there are Bmerous small, bluish-white macules. In addition, similar spots are noted rarely on the inner conjunctival folds of the eye or the vaginal mucosa. These hognomonic spots represent foci of epithelial necrosis and have been described as "grains of salt" on a red background. The height of the mucosal eruption occurs just as exanthem begins to develop and spread.

Koplik's spots are not the only oral manifestation that may be associated with measles. Candidiasis, necrotizing ulcerative gingivitis, and necrotizing stomatitis may occur if significant malnutrition also is present. Severe measles in early childhood can affect odontogenesis and result in pitted enamel hypoplasia of the developing permanent teeth. Enlargement of accessory lymphoid tissues such as the lingual and pharyngeal tonsils also may be noted.

Pathologic Features

Because of the reduced prevalence of measles and the transient nature of Koplik's spots, few oral and maxillofacial pathologists have had the opportunity to view these lesions microscopically. Initially, Koplik's spots represent areas of focal hyperparakeratosis in which the underlying epithelium exhibits spongiosis, intercellular edema, dyskeratosis, and epithelial syncytial giant cells. The number of nuclei within these giant cells ranges from 3 to over 25. Close examination of the epithelial cells often reveals pink-staining

inclusions in the nuclei or less commonly in the cytoplasm. Upon electron microscopy, the inclusions have been shown to represent microtubular aggregates characteristic of the causative paramyxovirus. As the spot ages, the epithelium exhibits heavy exocytosis by neutrophils leading to microabscess formation, epithelial necrosis, and, ultimately, ulceration. Frequently, examination of the epithelium adjacent to the ulceration will reveal the suggestive syncytial giant cells.

Examination of hyperplastic lymphoid tissue during the prodromal stage of measles often reveals a similar alteration. In 1931, Warthin and Finkeldey, in two separate publications, reported an unusual finding in patients who had their tonsils removed within 1 to 5 days of the clinical appearance of measles. Within the hyperplastic lymphoid tissue, there were numerous multinucleated giant lymphocytes. These multinucleated cells subsequently have been termed Warthin-Finkeldey giant cells and were thought for a time to be specific for measles. Since that time, however, similar-appearing cells have been noted in a variety of lymphoproliferative conditions such as lymphoma, Kimura's disease, AIDS-related lymphoproliferative disease, and lupus erythematosus.

Diagnosis

The diagnosis of typical measles in an epidemic setting usually is straightforward and based on the clinical features and history. Laboratory confirmation can be of value in isolated or atypical cases. Viral isolation or rapid detection of viral antigens is possible, but confirmation usually is established through a demonstration of rising serologic antibody titers. The antibodies appear within I to 3 days after the beginning of the exanthem and peak in about 3 to 4 weeks.

Treatment and Prognosis

With a complication rate of 21 %, the best treatment for measles is a good vaccination program; rubeola is part of the widely used MMR vaccine. In an attempt to stop the resurgence of measles that began in 1989, the vaccination schedule was altered and the pockets of young, unvaccinated children were targeted. This action brought the transmission of indigenous measles to record lows. Although the number is variable from year to year, since 1993, the annual incidence of reported cases in the United States typically is well below 500. Total eradication of the infection is technically feasible with existing vaccines but will require universal cooperation and enthusiasm from across the globe. Renewed emphasis in the noncompliant sections of society must be stressed. In addition, a new two-dose vaccination schedule has been adopted in an attempt to decrease the vaccine failures. Currently, routine vaccination is recommended for all children between the ages of 12 and 15 months, with a second dose administered between the ages of 4 and 6 years.

In otherwise healthy patients with measles, fluids and nonaspirin antipyretics are recommended for symptomatic relief. Immunocompromised patients also may be treated with one of a number of medications that have shown promise but definitively have not been proven to be efficacious. The most promising is ribavirin; however, immunoglobulin, interferon, and vitamin A also are being used.

RUBELLA (GERMAN MEASLES)

Rubella is a mild viral illness that is produced by a togavirus. The greatest importance of this infection lies not in its effects on those who contract the acute illness, but in its capacity to induce birth defects in the developing fetus. The virus is contracted through respiratory droplets, and it is transmitted to nearly 100% of individuals in close living conditions. The incubation time is from 14 to 21 days, and infected patients are contagious from 1 week before the exanthem to about 5 days after the development of the rash. Infants with a congenital infection may release virus for up to 1 year.

In the past, this infection occurred in cycles, with localized epidemics every 6 to 9 years and pandemics every 10 to 30 years. The last pandemic occurred from 1962 to 1964. In 1964 and 1965, the United States alone had more than 12.5 million cases, which resulted in more than 10,000 fetal deaths (direct effects or secondary to therapeutic abortions) and 20,000 infants born with congenital rubella syndrome (CRS).

An effective vaccine, first released in 1969, is used widely and has dramatically affected the epidemiology of the infection and broken the cycle of occurrences. The vaccine is contraindicated in the

following groups:

- Pregnant women
- Immunodeficient patients
- Patients with acute febrile illnesses
- Patients with a known allergy to components of the vaccine

It was postulated that the protection of children also would eliminate the risk of exposure to women in the childbearing years. A 99% decrease in the infection was seen between 1969 and 1988, but young adults remain susceptible. Like rubeola, 1989 and 1990 demonstrated a slight resurgence of rubella, which was the result of lack of vaccination diligence. More than 70% of the current cases occur in patients older than 15 years of age and 10% to 25% of young adults remain susceptible. Of course, this should change when the previously vaccinated children grow into adults. For the present, the vac- cination of postpubertal females must be stressed. Persons are presumed to be immune if they have received at least one dose of the MMR or were born before 1957. For pregnant females who have not received the vaccine, their immunity should be confirmed by demonstration of serum rubella IgG. Since 1992, the reported cases of indigenous rubella and CRS remain at a low and relatively constant level in the United States with less than 200 patients reported with rubella and no more than six infants affected with CRS annually.

Clinical Features

A large percentage of infections are asymptomatic; the frequency of symptoms is greater in adolescents and adults. Prodromal symptoms may be seen 1 to 5 days before the exanthem and include fever, headache, malaise, anorexia, myalgia, mild conjunctivitis, coryza, pharyngitis, cough, and lymphadenopathy. The lymphadenopathy may persist for weeks and is noted primarily in the suboccipital, postauricular, and cervical chains. The most common complication is arthritis, which increases in frequency with age and usually arises subsequent to the rash. Rare complications include encephalitis and thrombocytopenia.

The exanthematous rash is often the first sign of the infection and begins on the face and neck, with spread to the entire body within 1 to 3 days. The rash forms discrete pink macules, then papules, and finally fades with flaky desquamation. The rash fades as it spreads and often exhibits facial clearing before the completion of its spread into the lower body areas.

Oral lesions, known as Forchheimer's sign, have been reported to be present in about 20% of the cases. These consist of small, discrete, dark-red papules that develop on the soft palate and may extend onto the hard palate. This enanthem arises simultaneously with the rash becoming evident in about 6 hours after the first symptoms and not lasting longer than 12 to 14 hours. Palatal petechiae also may occur.

The risk of CRS correlates with the time of infection. The frequency of transmission from an infected mother is greater than 80% during the first 12 weeks of pregnancy, with the risk of fetal damage decreasing dramatically at 8 weeks and becoming rare after 20 weeks of gestation. The classic triad of CRS consists of deafness, heart disease, and cataracts. Deafness is the most common manifestation, affecting more than 80% of the patients. This hearing loss may not become evident until 2 years of age and usually is bilateral. Less common, late emerging complications include encephalopathy, mental retardation, diabetes mellitus, and thyroid disorders.

Diagnosis

The diagnosis of rubella is contingent on laboratory tests because the clinical presentation of the acquired infection typically subclinical, mild, or nonspecific. Although viral culture is possible, serologic analysis is the mainstay of diagnosis.

Treatment and Prognosis

Rubella is mild, and therapy usually is not required. Nonaspirin antipyretics and antipruritic medications may be useful in patients with significant fever or symptomatic cutaneous involvement. Passive immunity may be provided by the administration of human rubella immunoglobulin. If immunoglobulin is given within a few days of exposure, it decreases the severity of the infection. This therapy typically is reserved for pregnant patients who decline abortion. A two-dose vaccination schedule with the MMR is recommended, with the first dose between 12 and 15 months of age and a

second between 4 and 6 years of age. This schedule has effectively prevented major epidemics of rubella and CRS in the United States.

MUMPS (EPIDEMIC PAROTITIS)

Mumps is a paramyxovirus infection that primarily affected the salivary glands. As with measles and rubella, the epidemiology has been affected dramatically by the MMR vaccine. Before the advent of widespread vaccination, epidemics were seen every 2 to 5 years. The vaccine directed against mumps was released in 1967, but its use was not accepted nationally until 1977. At that time, vaccination became the norm for children 12 to 15 months of age. The vaccine has a success rate of 75 % to 95%. Most individuals born before 1957 are thought to have immunity from exposure to naturally occurring mumps virus. Although most authorities assume that natural infection is associated with lifelong immunity, rare cases of recurrent mumps have been well documented in patients with a confirmed history of prior natural infection. |

The incidence of mumps decreased by 98% and reached an all-time low in 1985. In 1986, resurgence developed. In the past, most cases occurred in children aged 5 to 9 years; during the resurgence, the disease was more prevalent in 10-to 19-year-old patients. Outbreaks have been reported in high schools, on college campuses, and in the workplace. This increased incidence has been attributed to lack of vaccination, not vaccine failure. Subsequently, in the early 1990s, isolated outbreaks were reported in highly vaccinated populations and thought to be the result of large-scale vaccination failure. Not long after these reports, a second immunization as part of the MMR vaccine was recommended at 4 to 6 years of age. When compared with the prevaccine era, the two-dose MMR vaccination schedule has reduced the prevalence of mumps by 99%. In addition, in an attempt to decrease the prevalence in the older age groups, it is recommended that individuals lacking a history of mumps or MMR vaccination be immunized. This primarily affects those born between 1967 and 1977 and, to a lesser extent, those born between 1957 and 1967.

The mumps virus can be transmitted through urine, saliva, or respiratory droplets. The incubation period usually is 16 to 18 days, with a range of about 2 to 4 weeks. Patients are contagious from 1 day before the clinical appearance of infection to 14 days after its clinical resolution.

Clinical Features

Approximately 30% of mumps infections are subclinical. In symptomatic cases, prodromal symptoms of low-grade fever, headache, malaise, anorexia, and myalgia arrive first. Most frequently, these nonspecific findings are followed within 1 day by significant salivary gland changes. The parotid gland is involved most frequently, but the sublingual and submandibular glands also can be affected. Discomfort and swelling develop in the tissues surrounding the lower half of the external ear and extending down along the posterior inferior border of the adjacent mandible. The enlargement typically peaks within 2 to 3 days, and the pain is most intense during this period of maximal enlargement. Chewing movements of the jaw or eating saliva-stimulating foods tends to increase the pain. Enlargement of the glands usually begins on one side and is followed by contralateral glandular changes within a few days. Unilateral involvement is seen in about 25% of patients.

The second most common finding is epididymoorchitis, which occurs in about 25% of postpubertal males. In those affected, the testicle exhibits rapid swelling with significant pain and tenderness. The enlargement can range from a minimal swelling to a fourfold increase in size. Unilateral involvement is most common. On resolution of the swelling, atrophy occurs in the affected testicle. Permanent sterility from testicular changes is rare. Less commonly, oophoritis and mastitis can be seen in postpubertal females. In addition, spontaneous abortion occurs in approximately 25% of females who contract mumps during the first trimester of pregnancy.

Less commonly, meningoencephalitis, cerebellar ataxia, hearing loss, pancreatitis, arthritis, carditis, and decreased renal function may occur. Isolated changes, such as orchitis or meningitis, may occur in the absence of salivary gland involvement, thereby making diagnosis difficult in nonepidemic settings. Mumps-related mortality is exceedingly rare and most frequently associated with mumps encephalitis.

The most frequently reported oral manifestation is redness and enlargement of Wharton's and Stensen's salivary gland duct openings. In addition, involvement of the sublingual gland may produce

bilateral enlargements of the floor of the mouth.

Diagnosis

The diagnosis of mumps can be made easily from the clinical presentation when the infection is occurring in an epidemic fashion; however, isolated cases must be differentiated from other causes. Saliva, urine, or cerebrospinal fluid specimens can be obtained for culture. The most frequently used confirmatory measures are demonstration of mumps-specific IgM or a fourfold rise of mumps-specific IgG liters when measured during the acute phase and about 2 weeks later.

Treatment and Prognosis

The treatment of mumps is palliative in nature. Frequently, nonaspirin analgesics and antipyretics are administered. In an attempt to minimize orchitis, bed rest is recommended for males until the fever breaks. Avoidance of sour foods and drinks helps to decrease the salivary gland discomfort. As with measles and rubella, the best results come from prior vaccination, thereby preventing the infection.

LECTURE 4
FUNGAL AND PROTOZOAL DISEASES

CANDIDIASIS

Infection with the yeastlike fungal organism *Candida alblicans* is termed candidiasis or, as the British prefer, candidosis. An older name for this disease is moniliasis; the use of this term should be discouraged because it is derived from the archaic designation *Monilia albicans.* Other members of the *Candida* genus, such as C. *tropi-colls,* C. *krusel, C. parapsilosis,* and C. *gullliierniondi,* may also be found intraorally, but they rarely cause disease.

Like many other pathogenic fungi, C. *albicatis* may exist in two forms, a trait known as dimorphism. The yeast form of the organism is believed to be relatively innocuous, but the hyphal form is usually associated with invasion of host tissue.

Candidiasis is by far the most common oral fungal infection in humans and has a variety of clinical manifestations, making the diagnosis difficult at times. In fact, C. *albicans* may be a component of the normal oral microflora, with as many as 30% to 50% of people simply carrying the organism in their mouths without clinical evidence of infection. This rate of carriage has been shown to increase with age, and C. *albicans* can be recovered from the mouths of nearly 60% of dentate patients over the age of 60 years who have no sign of oral mucosal lesions. At least three general factors may determine whether clinical evidence of infection exists:

1. The immune status of the host
2. The oral mucosal environment
3. The strain of C. *albicans*

In the past, candidiasis was considered to be only an opportunistic infection, affecting individuals who were debilitated by another disease. Certainly, such patients make up a large percentage of those with candidal infections today. However, now clinicians recognize that oral candidiasis may develop in people who are otherwise healthy. As a result of this complex host and organism interaction, candidal infection may range from mild, superficial mucosal involvement seen in most patients to fatal, disseminated disease in severely immunocompromised patients. This chapter focuses on those clinical presentations of candidiasis that affect the oral mucosa.

Clinical Features

Candidiasis of the oral mucosa may exhibit a variety of clinical patterns. Many patients will display a single pattern, although some individuals will exhibit more than one clinical form of oral candidiasis.

Pseudomembranous taiididiasis. The best recognized form of candidal infection is pseudomembranous candidiasis. Also known as "thrush," pseudomembranous candidiasis is characterized by the presence of adherent white plaques that resemble cottage cheese or curdled milk on the oral mucosa. The white plaques arc composed of tangled masses of hyphae, yeasts, desquamated epithelial cells, and debris. Scraping them with a tongue blade or rubbing them with a dry gauze sponge can remove these plaques. The underlying mucosa may appear normal or erythcmatous. If bleeding occurs, the mucosa has probably also been affected by another process, such as lichen planus or cancer chemotherapy.

Pseudomembranous candidiasis may be initiated by exposure of the patient to broad-spectrum antibiotics (thus eliminating competing bacteria) or by impairment of the patient's immune system. The immune dysfunctions seen in leukcmic patients or those infected with human immunodeficiency virus (HIV) are often associated with pseudomembranous candidiasis. Infants may also be affected, ostensibly because of their underdeveloped immune system. Antibiotic exposure is typically responsible for an acute (rapid) expression of the condition; immunologic problems usually produce a chronic (slow-onset, longstanding) form of pseudomembranous candidiasis.

Symptoms, if present at all, are usually relatively mild, consisting of a burning sensation of the oral mucosa or an unpleasant taste in the mouth, variably described as salty or bitter. Sometimes patients complain of "blisters," when in fact they feel the elevated plaques rather than true vesicles. The plaques are characteristically distributed on the buccal mucosa, palate, and dorsal tongue.

Etythtmatous candidiasis. In contrast to the pseudomembranous form, patients with crythematous candidiasis cither do not show white flecks or a white component is not a prominent feature. Several clinical presentations may be seen. The first, known as acute atrophic candidiasis or "antibiotic sore mouth," typically follows a course of broad-spectrum antibiotics. Patients often complain that their mouth feels as if a hot beverage had scalded it. This burning sensation is usually accompanied by a diffuse loss of the filiform papillae of the dorsal tongue, resulting in a reddened, "bald" appearance of the tongue.

Other forms of erythcmatous candidiasis are usually asymptomatic and chronic.

Included in this category is the condition known as central papillary atrophy of the tongue, or median rhomboid glossitis, in the past, this was thought to be a developmental defect of the tongue, occurring in 0.01% to 1,00% of adults. The lesion was supposed to have resulted from a failure of the embryologic tuberculum impar to be covered by the lateral processes of the tongue. Theoretically, the prevalence of central papillary atrophy in children should be identical to that seen in adults; however, in one study in which 10,000 children were examined, not a single lesion was detected. Other investigators have noted a consistent re-lationship between the lesion and C. *albicans,* and similar lesions have been induced experimentally on the dorsal tongues of rats.

Clinically, central papillary atrophy appears as a well-demarcated erythematous zone that affects the midline, posterior dorsal tongue and often is asymptomatic. The erythema is due in part to the loss of the filiform papillae in this area. The lesion is usually symmetric, and its surface may range from smooth to lobulated. Often the mucosal alteration resolves with antifungal therapy, although occasionally only partial resolution can be achieved.

Some patients with central papillary atrophy may also exhibit signs of oral mucosal candidal infection at other sites. This presentation of erythematous candidiasis has been termed chronic multifocal candidiasis. In addition to the dorsal tongue, the sites that show involvement include the junction of the hard and soft palate and the angles of the mouth. The palatal lesion appears as an erythematous area that, when the tongue is at rest, contacts the dorsal tongue lesion, resulting in what is called a "kissing lesion" because of the intimate proximity of the involved areas.

The involvement of the angles of the mouth (angular cheilitis,perleche) is characterized by erythema, fissuring, and scaling. Sometimes this condition is seen as *3* component of chronic multifocal candidiasis, but it often occurs alone, typically in an older person with reduced vertical dimension of occlusion and accentuated folds at the corners of the mouth. Saliva tends to pool in these areas, keeping them moist and thus favoring a yeast infection. Patients often indicate that the severity of the lesions waxes and wanes. Micro biologic studies have indicated that 20% of these cases are caused by *C. albicans* alone, 60% are due to a combined infection with C. *albicans* and *Staphyiacoccus aureus,* and 20% are associated with S. *aureus* alone. Infrequently, the candidal infection more extensively involves the peri-oral skin, usually secondary to actions that keep the skin moist (e.g., chronic lip licking, thumb sucking), creating a clinical pattern known as cheilocandidiasis. Other causes of exfoliativc cheilitis often must be considered in the differential diagnosis. Denture stomatitis should be mentioned because it is often classified as a form of erythematous candidiasis, and the term chronic atrophic candidiasis may be used synonymously by some authors. This condition is characterized by varying degrees of erythema, sometimes accompanied by petechial hemorrhage, localized to the denture-bearing areas of a maxillary removable dental prosthesis. Although the clinical appearance can be striking, the process is rarely symptomatic. Usually the patient admits to wearing the denture continuously, removing it only periodically to clean it. Whether this represents actual infection by C. *albicans* or is simply a tissue response by the host to the various microorganisms living beneath the denture remains controversial. The clinician should also rule out the possibility that this reaction could be caused by improper design of the denture (which could cause unusual pressure on the mucosa), allergy to the denture base, or inadequate curing of the denture acrylic.

Although C. *albicans* is often associated with this condition, biopsy specimens of denture stomatitis seldom show candidal hyphae actually penetrating the keratin layer of the host epithelium. Therefore, one of the main defining criteria for the diagnosis of infection—host tissue invasion by the organism—is not met by this lesion. Furthermore, if the palatal mucosa and tissue-contacting surface of the denture are swabbed and separately streaked onto a Sabouraud's agar slant, the denture typically shows much heavier colonization by yeast.

Chronic hyperplastic candidiasis (candidal leukoplakia). In some patients with oral candidiasis, there may be a white patch that cannot be removed by scraping; in this case the term chronic hyperplastic candidiasis is appropriate. This form of candidiasis is the least common and *is* also somewhat controversial. Some investigators believe that this condition simply represents candidiasis that is superimposed on a preexisting leukoplakic lesion, a situation that may certainly exist at times. In some instances, however, the candidal organism alone may be capable of inducing a hyperkeratotic lesion. Such lesions are usually located on the anterior buccal mucosa and cannot clinically be distinguished from a routine leukoplakia. Often the leukoplakic lesion associated with candidal infection has a fine intermingling of red and white areas, resulting in a speckled leukoplakia. Such lesions may have an increased frequency of epithelial dysplasia histopathologically.

The diagnosis is confirmed by the presence of candidal hyphae associated with the lesion and by complete resolution of the lesion after antifungal therapy.

Macocutaneous candidiasis. Severe oral candidiasis may also be seen as a component of a relatively rare group of immunologic disorders known as *mucocutaneous candidiasis.* Several distinct immunologic dysfunctions have been identified, and the severity of the candidal infection correlates with the severity of the immunologic defect. Most cases are sporadic, although an autosomal recessive pattern of inheritance has been identified in some families. The immune problem usually becomes evident during the first few years of life, when the patient begins to have candidal infections of the mouth, nails, skin, and other mucosal surfaces. The oral lesions appear as thick, white plaques that typically do not rub off (essentially chronic hyperplastic candidiasis).

Patients should be evaluated periodically because any one of a variety of endocrine abnormalities **(cndocrine-candidiasis syndrome),** as well as iron-deficiency anemia, may develop in addition to the candidiasis. These endocrine disturbances include hypothyroidism, hypoparathyroidism, hypoadrenocorticism (Addison's disease), and diabetes mellirus. Typically, the endocrine abnormality develops months or even years after the onset of the candidal infection. Interestingly, the candidal infection remains relatively superficial rather than disseminating throughout the body. Both the oral lesions and the rather grotesque, roughened, foul-smelling cutaneous plaques and nodules can be controlled with continuous use of relatively safe systemic antifungal drugs.

Histopathologic Features

The candidal organism can be seen microscopically in either an exfoliative cytologic preparation or in tissue sections obtained from a biopsy specimen. On staining with the periodic acid-Schiff (PAS) method, the candidal hyphae and yeasts can be readily identified. The PAS method stains carbohydrates, contained in abundance by fungal cell walls; the organisms are easily identified by the bright magenta color imparted by the stain. To make a diagnosis of candidiasis, one must be able to see hyphae or pseudohyphac (which are essentially elongated yeast cells). These hyphae are approximately 2 µm in diameter, vary in their length, and may show branching. Often the hyphae are accompanied by variable numbers of yeasts, squamous epithelial cells, and inflammatory cells.

A 10% to 20% potassium hydroxide (KOH) preparation may also be used to rapidly evaluate specimens for the presence of fungal organisms. With this technique, the KOH lyses the background of epithelial cells, allowing the more resistant yeasts and hyphae to be visualized.

The disadvantages of the KOH preparation include the following:

- Lack of a permanent record
- Greater difficulty in identifying the fungal organisms, compared with PAS staining
- Inability to assess the nature of the epithelial cell population with respect to other conditions, such as epithelial dysplasia or pemphigus vulgaris

The histopathologic pattern of oral candidiasis may vary slightly, depending on which clinical form of the infection has been submitted for biopsy. The features that are found in common include an increased thickness of parakeratin on the surface of the lesion in conjunction with elongation of the epithelial rete ridges. Typically, a chronic inflammatory cell infiltrate can be seen in the connective tissue immediately subjacent to the infected epithelium, and small collections of neutrophils (microabscesses) are often identified in the parakeratin layer and the superficial spinous cell layer near the organism. The candidal hyphae are embedded in the parakeratin layer and rarely penetrate into the viable cell layers of the epithelium unless the patient is extremely immunocompromised.

Diagnosis

The diagnosis of Candidiasis in clinical practice is usually established by the clinical signs in conjunction with exfolialive cytologic examination. Although a culture can definitively identify the organism as *C. albicans.* this process may not be practical in most office settings. The cytologic findings should demonstrate the hyphal phase of the organism, and antifungal therapy can then be instituted. If the lesion is clinically suggestive of chronic hyperplastic candidiasis but does not respond to antifungal therapy, a biopsy should be performed lo rule out the possibility of C. *albicans* superimposed on epithelia.1 dysplasia, squamous cell carcinoma, or lichen planus.

The definitive identification of the organism can be made by means of culture. A specimen for culture is obtained by rubbing a sterile cotton swab over the lesion and then streaking the swab on the surface of a Sabouraud's agar slant. C. *albicans* will grow as creamy, smooth-surfaced colonies after 2 to 3 days of incubation at room temperature.

Treatment and Prognosis

Several antifungal medications have been developed for managing oral candidiasis, each with its advantages and disadvantages.

Polyene agents

Nystatin. In the 1950s, the polyene antibiotic nystatin was the first effective Ireatment for oral candidiasis. Nystatin is formulated for oral use as a suspension or pastille (lozenge). Many patients report that nystatin has a very bitter taste, which may reduce patient compliance; therefore, the taste has to be disguised with sucrose and flavoring agents. If the candidiasis is due to xerostomia, the sucrose content of the nystatin preparation may contribute to xerostomia-related caries in these patients. The gastrointestinal tract poorly absorbs both nystatin and the other polyene antibiotic, amphotericin; therefore, their effectiveness depends on direct contact with the candidal organisms. This necessitates multiple daily doses so that the yeasts are adequately exposed to the drug. Nystatin combined with triamcinolone acetonide cream or ointment can be applied topically and is effective for angular cheilitis that does not have a bacterial component.

Amphotericin B. For many years in the United States, the use of amphotericin B was restricted to intravenous treatment of life-threatening systemic fungal infections. This medication subsequently became available as an oral suspension for the management of oral candidiasis. Unfortunately, the interest in this formulation of the drug was scant, and it is no longer marketed in the United States.

Imidazole agents. The imldazole-derived antifungal agents were developed during the 1970s and represented a major step forward in the management of candidiasis. The two drugs of this group that are used most frequently are clotrimazole and ketoconazole.

Clotrimazole. Like nystatin, clotrimazole is not well absorbed and must be administered several times each day. It is formulated as a pleasant-tasting troche (lozenge) and produces few side effects. Clotrimazole cream is also effective treatment for angular cheilitis because this drug has antibacterial and antifungal properties.

Ketoconazole. Ketoconazole was the first antifungal drug that could be absorbed across the gastrointestinal tract, thereby providing systemic therapy by an oral route of administration. The single daily dose was much easier for the patient to use; however, several disadvantages have been noted. Patients must not take antacids or H_2-blocking agents because an acidic environment is required for proper absorption. If a patient is to take ketoconazole for more than 2 weeks, liver function studies are recommended because approximately 1 in 10,000 individuals will experience idiosyncratic liver toxicity from the agent. For this reason, the U.S. Food and Drug Administration has stated that ketoconazole should not be used as initial Iherapy for routine oral candidiasis. Furthermore, ketoconazole has been implicated in drug Interactions with the macrolide antibiotics (e.g., erythromycin), the gastrointestinal motility-enhancing agent cisapridc, and theantihistamine astemizole, all of which may produce potentially life-threatening cardiac arrhythmias.

Triazole agents. The triazoles are the newest group of antifungal drugs. Both fluconazole and itraconazolc have been approved for treat ing candidiasis in the United States.

Fluconazole. Fluconazole appears to be more effective than ketoconazole; it is well absorbed systemically, and an acidic environment is not required for absorption. A relatively long half-life allows for once-daily dosing, and liver toxicity is rare at the doses used to treat oral candidiasis. Some reports have suggested that fluconazole may not be appropriate for long-term preventive therapy because resistance to the drug seems to develop in some instances. Known drug interactions include a potentia-tion of the effects of phcnytoin (Dilantin), an antiselzure medication; warfarin compounds (anticoagulants); and sulfonylureas (oral hypoglycemic agents).

Itracotiazole. Itraconazole has proven efficacy against a variety of fungal diseases, including histoplasmosis, blas-tomycosis, and fungal conditions of the nails. Recently, itraconazole solution was approved for management of oropharyngeal candidiasis, and this appears to have an efficacy equivalent to clotrimazole and fluconazole. As with fluconazole, significant drug interactions are possible, and itraconazole is contra indicated for patients taking astemizole, triazolam, midazolam, and cisapride.

Other antifungal agents

Iodoquinol. Although not strictly an antifungal drug, lodoquinol has antifungal and antibacterial properties. When compounded in a cream base with a corticosteroid, this material is very effective as topical therapy for angular chellitis.

In most cases, oral candidiasis is an annoying superficial infection that is easily resolved by antifungal therapy. If infection should recur after treatment, a thorough investigation of potential factors that could predispose to candidiasis, including immunosuppression, may be necessary. In only the most severely compromised patient will candidiasis cause deeply invasive disease.

HISTOPLASMOSIS

Histoplasmosis, the most common systemic fungal infection in the United States, is caused by the organism *Histoplasma capsulation.* Like several other pathogenic fungi, *H. capsulatum* is dimorphic, growing as a yeast at body temperature in the human host and as a mold in its natural environment. Humid areas with soil enriched by bird or bat excrement are especially suited to the growth of this organism. This habitat preference explains why histoplasmosis is seen endemically in fertile river valleys, such as the region drained by the Ohio and Mississippi Rivers in the United States. Airborne spores of the organism are inhaled, pass into the terminal passages of the lungs, and germinate.

Approximately 500,000 new cases of histoplasmosis are thought to develop annually in the United States; other parts of the world, such as Central and South America, Europe, and Asia, also report numerous cases. Epidemiologic studies in endemic areas of the United States suggest that 80% to 90% of the population in these regions has been infected.

Clinical *and* Radiographic Features

Most cases of histoplasmosis produce either no symptoms or such mild symptoms that the patient does not seek medical treatment. The expression of disease depends on the quantity of spores inhaled, the immune status of the host, and perhaps the strain of H. *capsulatum.* Most individuals who become exposed to the organism are relatively healthy and do not inhale a large number of spores; therefore, they have either no symptoms or they have a mild, flulike illness for 1 to 2 weeks. The inhaled spores are ingested by macrophages within 24 to 48 hours, and specific T-lymphocyte immunity develops in 2 to 3 weeks. Antibodies directed against the organism usually appear several weeks later. With these defense mechanisms, the host is usually able to destroy the invading organism, although sometimes the macrophages simply surround and confine the fungus so that viable organisms can be recovered years later. Thus, patients who formerly lived in an endemic area may have acquired the organism and later express the disease at some other geographic site if they become immunocompromised.

Acute histoplasmosis is a self-limited pulmonary infection that probably develops in only about 1% of people who arc exposed to a low number of spores. With a high concentration of spores, as many as 50% to 100% of individuals may experience acute symptoms. These symptoms (e.g., fever, headache, myalgia, nonproductive cough, anorexia) result in a clinical picture similar to that of influenza. Patients are usually ill for 2 weeks, although calcification of the hilar lymph nodes may be detected as an incidental finding on chest radiographs years later.

Chronic histoplasmosis also primarily affects the lungs, although it is much less common than acute histoplasmosis. The chronic form usually affects elderly, emphysematous, white men or immunosuppressed patients. Clinically, it appears similar to tuberculosis. Patients typically exhibit cough, weight loss, fever, dyspnea, chest pain, hemoptysis, weakness, and fatigue. Chest rocntgenograms show upper-lobe infiltrates and cavitation.

Disseminated histoplasmosis is even less common than the acute and chronic types. It occurs in I of 2000 to 5000 patients who have acute symptoms. This condition is characterized by the progressive spread of the infection to extrapulmonary sftes. It usually occurs in either older, debilitated, or immunosuppressed patients, in some areas of the United States, from 2% to 10% of patients with acquired immunodeficiency syndrome (AIDS) develop disseminated histoplasmosis. Tissues that may be affected include the spleen, adrenal glands, liver, lymph nodes,

gastrointestinal tract, central nervous system (CNS), kidneys, and oral mucosa. Adrenal involvement may produce hypoadrenocorticism (Addison's disease).

Most oral lesions of histoplasmosis occur with the disseminated form of the disease. The most commonly affected sites are the tongue, palate, and buccal mucosa. The condition usually appears as a solitary, variably painful ulceration of several weeks' duration; however, some lesions may appear erythematous or white with an irregular surface. The ulcerated lesions have firm, rolled margins, and they may be indistinguishable clinically from a malignancy.

Histopathologic Features

Microscopic examination of lesional tissue shows either a diffuse infiltrate of macrophages or, more commonly, collections of macrophages organized into granulomas. Multinucleated giant cells are usually seen in association with the granulomatous inflammation. The causative organism can be identified with some difficulty in the routine hematoxylin and eosin-stained section; however, special stains, such as the PAS and Grocott-Gomori methenamine silver methods, readily demonstrate the characteristic l - to 2-μm yeasts of *H. cap-sulatum*.

Diagnosis

The diagnosis of histoplasmosis can *be* made by histopathologic identification of the organism in tissue sections or by culture. Other helpful diagnostic studies include serologic testing in which antibodies directed against *H. capsulatum* are demonstrated and antigen produced by the yeast is identified.

Treatment and Prognosis

Acute histoplasmosis, because it is a self-limited process, generally warrants no specific treatment other than supportive care with analgesics and antipyretics. Often the disease is not treated because the symptoms are so nonspecific and the diagnosis is not readily evident.

Patients with chronic histoplasmosis usually require treatment, despite the fact that up to half of them may recover spontaneously. Often the pulmonary damage is progressive if it remains untreated, and death may result in up to 20% of these cases. The treatment of choice is intravenous amphotericin B, although significant kidney damage can result from this therapy. For that reason, ketoconazole may be used in nonimmunosuppressed patients because it is associated with fewer side effects. The triazole compound itraconazole can also be used for treatment of histoplasmosis. This agent appears to be more effective than ketoconazole and less likely to produce toxicity.

Disseminated histoplasmosis is a very serious condition that results in death in 90% of the patients if they remain untreated. Amphotericin B is usually indicated for such patients. Despite therapy, however, a mortality rate of 7% to 23% is observed. Itraconazole or ketoconazole may also be used if the patient is nonimmuno-compromised; however, the response rate is slower than for patients receiving amphotericm B, and the relapse rate may be higher.

BLASTOMYCOSIS

Blastomycosis is a relatively uncommon disease caused by the dimorphic fungus known as *Biaslomyces dermatitis.* Although the organism is rarely isolated from its natural habitat, it seems to prefer rich, moist soil, where it grows as a mold. Much of the region in which it grows overlaps the territory associated with H. *capsulatmn* (affecting the eastern ha If of the United States). The range of blastomycosis extends farther north, however, including Wisconsin, Minnesota, and the Canadian provinces surrounding the Great Lakes. Sporadic cases have also been reported in Africa, India, Europe, and South America. By way of comparison, histoplasmosis appears to be at least 10 times more common than blastomycosis. In several series of cases, a prominent adult male predilection has been noted, often with a male-to-female ratio as high as 9:1. This has been attributed to the greater degree of outdoor activity (e.g., hunting, fishing) by men in areas where the organism grows. The occurrence of blastomycosis in immunocompromised patients is relatively rare.

Clinical and Radiographic Features

Blastomycosis is almost always acquired by inhalation of spores, particularly after a rain. The spores reach the alveoli of the lungs, where they begin to grow as yeasts at body temperature. In most patients, the infection is probably halted and contained in the lungs, but it may become hematogenously disseminated in a few instances. In order of decreasing frequency, the sites of dissemination include skin, bone, prostate, meninges, oropharyngeal mucosa, and abdominal organs.

Although most cases of blastomycosis are either asymptomatic or produce only very mild symptoms, patients who do experience symptoms usually have pulmonary complaints. Acute blastomycosis resembles pneumonia, characterized by high fever, chest pain, malaise, night sweats, and productive cough with mucopurulent sputum. Rarely, the infection may precipitate life-threatening adult respiratory distress syndrome.

Chronic blastomycosis is more common than the acute form, and it may mimic tuberculosis; both conditions are often characterized by low-grade fever, night sweats, weight loss, and productive cough. Chest radiographs may appear normal, or they may demonstrate diffuse infiltrates or one or more pulmonary or hilar masses. Unlike the situation with tuberculosis and histoplasmosis, calcification is not typically present. Cutaneous lesions usually represent the spread of infection from the lungs, although occasionally they are the only sign of disease. Such lesions begin as erythematous nodules that enlarge, becoming verrucous or ulcerated.

Oral lesions of blastomycosis may result from either cxtrapulmonary dissemination or local inoculation with the organism. These lesions may have an irregular, erythematous or white intact surface, or they may appear as ulccrations with irregular rolled borders and varying degrees of pain. Clinically, because the lesions resemble squamous cell carcinoma, biopsy and histopathologic examination are required.

Hlstopathologic Features

Histopathologic examination of lesional tissue typically shows a mixture of acute inflammation and granulomatous inflammation surrounding variable numbers of yeasts. These organisms are 8 to 20 μm in diameter.

They are characterized by a doubly retractile cell wall and a broad attachment between the budding daughter cell and the parent cell. Like many other fungal organisms, *B. dermatitidis* can be detected more easily using special stains, such as the Grocott-Gomori methenamine silver and PAS methods. Identification of these organisms is especially important because this infection often induces a benign reaction of the overlying epithelium in mucosal or skin lesions called pseudoepitheliomatous (pseudocarcinomatous) hyperplasia.

Because this benign elongation of the epithelial rete ridges may look like squamous cell carcinoma at first glance under the microscope, careful inspection of the underlying inflamed lesional tissue is mandatory.

Diagnosis

Rapid diagnosis of blastomycosis can be performed by microscopic examination of cither histopathologic sections or an alcohol-fixed cytologic preparation. The most rapid means of diagnosis, however, is the KOH preparation, which may be used for examining scrapings from a suspected lesion. The most accurate method of identifying B. *dermatitidis* is by obtaining a culture specimen from sputum or fresh biopsy material and growing the organism on Sabouraud's agar. This is a slow technique, however, sometimes taking as long as 3 to 4 weeks for the characteristic mycclium-to-yeast conversion to take place. A specific DNA probe has been developed, allowing immediate identification of the mycelial phase that usually appears by 5 to 7 days in culture. Serologic studies are usually not helpful.

Treatment and Prognosis

As stated previously, most patients with blastomycosis require no treatment. Even in the case of symptomatic acute blastomycosis, administration of systemic amphotericin B is indicated only if the patient:

- Is seriously ill,
- Is not improving clinically, or
- Is ill for more than 2 or 3 weeks.

Patients with chronic blastomycosis or extrapulmonary lesions need treatment. Itraconazole is generally recommended, particularly if the infection is mild or moderate. Although ketoconazolc is active against *B. dcrmatitidis,* it has been shown to be less effective than itraconazole. Ampholericin B is reserved for patients who are severely ill or show no response to itraconazole.

Disseminated blastomycosis occurs in only a small percentage of infected patients and, with proper treatment, the outlook for the patient is reasonably good.

PARACOCCIDIOIDOMYCOSIS (SOUTH AMERICAN BLASTOMYCOSIS)

Pa racocc id Joi do mycosis is a deep fungal infection that is caused by *Paracoccidioides brasiliensts.* The condition is seen most frequently in patients who live in either South America (primarily Brazil, Colombia. Venezuela, Uruguay, and Argentina) or Central America. However, immigrants from those regions and visitors to those areas can acquire the infection. Within some endemic areas, the nine-banded armadillo recently has been shown to harbor P. *brasilicnsis* (similar to the situation seen with leprosy). Although there is no evidence that the armadillo directly infects humans, it may be responsible for the spread of the organism in the environment.

Paracoccidioidomycosis has a distinct predilection for males, with a 25:1 malcto-female ratio typically reported. This striking difference is thought to be attributable to a protective effect of female hormones (because beta-estradiol inhibits the transformation of the hyphal form of the organism to the pathogenic yeast form). This theory is supported by the finding of an equal number of men and women who have antibodies directed against the yeast.

Clinical Features

Patients with paracoccidioidomycosis are typically middle-aged at the time of diagnosis, and most are employed in agriculture. Most cases of paracoccidioidomycosis are thought to appear initially as pulmonary infections after exposure to the spores of the organism. Although infections are generally self-limiting, P. *bras-iliensis* may spread by a hematogenous or lymphatic route to a variety of tissues, including lymph nodes, skin, and adrenal glands. Adrenal involvement often results In hypoadrenocorticism (Addisun's disease). Oral lesions appear as mulberry-like ulcerations that most commonly affect the alveolar mucosa, gingiva, and palate. The lips, oropharynx. and buccal mucosa are also involved in a significant percentage of cases. In most patients with oral lesions, more than one oral mucosal site is affected.

Histopathologic Features

Microscopic evaluation of tissue obtained from an oral lesion may reveal pseudoepitheliomatous hyperplasia in addition to ulceration of the overlying surface epithelium. P. *brastliensis* elicits a granulomatous inflammatory host response that is characterized by collections of epithelioid macrophages and multinucleated giant cells. Scattered, large (up to 30 μm in diameter) yeasts are readily identified after staining of the tissue sections with the Grocott-Gomori methenamine silver or PAS method. The organisms often show multiple daughter buds on the parent cell, resulting in an appearance

that has been described as resembling "Mickey Mouse ears" or the spokes of a ship's steering wheel ("mariner's wheel").

Diagnosis

Demonstration of the characteristic multiple budding yeasts in the appropriate clinical setting is usually adequate to establish a diagnosis of paracoccidioidomycosis. Specimens for culture can be obtained, but R *brasiliensis* grows quite slowly.

Treatment and Prognosis

The method of management of patients with paracoccidioidomycosis depends on the severity of the disease presentation. Sulfonamide derivatives have been used since the 194Qs to treat this infection. These drugs are still used today in many instances to treat mi Id-to-moderate cases, particularly in developing countries with limited access to the newer, more expensive antifungal agents. For severe involvement, intravenous amphotericin B is usually indicated. Cases that are not life-threatening are best managed by oral itraconazole, although therapy may be needed for several months. Ketoconazole can also be used, although the side effects are typically greater than those associated with itraconazole.

COCCIDIOIDOMYCOSIS (SAN JOAQUIN VALLEY FEVER; VALLEY FEVER; COCCI)

Coccidioides immitis is the fungal organism responsible for coccidioidomycosis. C. *immitis* grows saprophytically in the alkaline, semiarid, desert soil of the southwestern United States and Mexico, with isolated regions also noted in Central and South America. As with several other pathogenic fungi, C. *immitis* is a dimorphic organism, appearing as a mold in its natural environment of the soil and as a yeast in tissues of the infected host. Arthrospores produced by the mold become airborne and can be inhaled into the lungs of the human host, producing infection.

Coccidioidomycosis is confined to the Western hemisphere and is endemic throughout the desert regions of southwestern United States and Mexico; however, with modern travel taking many visitors to and from the sunbelt, this disease can be encountered virtually anywhere in the world. It is estimated that 100,000 people are infected annually in the United States, although 60% of this group are asymptomatic.

Clinical Features

Most infections with C. *immitis* are asymptomatic, although approximately 40% of infected patients experience a flulike illness and pulmonary symptoms within I to 3 weeks after inhaling the arthrospores. Fatigue, cough, chest pain, myalgias, and headache are commonly reported, lasting several weeks with spontaneous resolution in most cases. Occasionally, the immune response may trigger a hypersensitivity reaction that causes the development of erythema multiforme or erythema nodosum. Erythema nodosum is characterized by the appearance of multiple painful erythematous inflammatorv nodules in the subcutaneous connective tissue. This hypersensitivity reaction occurring in conjunction with coccidioidomycosis is termed valley fever, and it resolves as the host cell-mediated immune response controls the pulmonary infection.

Chronic progressive pulmonary coccidioidomycosis is relatively rare. It mimics tuberculosis, with its clinical presentation of persistent cough, hemoptysis, chest pain, low-grade fever, and weight loss.

Disseminated coccidioidomycosis occurs when the organism spreads hematogenously to extrapulmonary sites. This occurs in less than 1 % of the cases, but it is a more serious problem. The most commonly involved areas include skin, lymph nodes, bone and joints, and the meninges. Immunosuppression greatly increases the risk of dissemination. The following groups are particularly susceptible:

- Patients taking large doses of systemic cortico-stcroids (organ transplant recipients)

- Patients being treated with cancer chemotherapy
- Patients in the end stages of HIV infection

Infants and older patients, both of whom may have suboptimally functioning immune systems, also may be at increased risk for disseminated disease. Persons of color (e.g., blacks, Filipinos, native Americans) also seem to have an increased risk, but it is unclear whether their susceptibility is due to genetic causes or socioeconomic factors, such as poor nutrition.

The cutaneous lesions may appear as papules, subcutaneous abscesses, verrucous plaques, and granulomatous nodules. Of prime significance to the clinician is the predilection for these lesions to develop in the area of the central face, especially the nasolabial fold. Oral lesions are distinctly uncommon.

Histopathologic Features

Biopsy material shows large (20 to 60 μm), round spherules that may contain numerous endospores. The host response may be variable, ranging from a suppurative, neutrophilic infiltrate to a granulomatous inflammatory response. In some cases, the two patterns of inflammation are seen concurrently. Special stains, such as the PAS and Grocott-Gomori methenamine silver methods, enable the pathologist to identify the organism more readily.

Diagnosis

The diagnosis of coccidioidomycosis can be confirmed by culture or identification of characteristic organisms in biopsy material. Cytologic preparations from bronchial swabbings or sputum samples may also reveal the organisms.

Serologic studies are helpful in supporting the diagnosis, and they may be performed at the same time as skin testing. Skin testing by itself may be of limited value in determining the diagnosis because many patients in endemic areas have already been exposed to the organism and have positive test findings.

Treatment

The decision whether or not to treat *a* particular patient affected by coccidioidomycosis depends on the severity and extent of the infection and the patient's immune status. Relatively mild symptoms in an immunocompetent person do not warrant treatment. Amphotericin B is administered for the following groups:

- Immunosuppressed patients
- Patients with severe pulmonary infection
- Patients who have disseminated disease
- Patients who appear to be in a life-threatening situation concerning the infection

For many cases of coccidioidomycosis, fluconazolc is the drug of choice, usually given in high doses for an extended period of time. Although the response of the disease to fluconazolc may be somewhat slower than that of amphotericin B, the side effects and complications of therapy are far fewer. Kctoconazole may be used as an alternative treatment for mild-to-moderate cases of coccidioidomycosis.

CRYPTOCOCCOSIS

Cryptococcosis is a relatively uncommon fungal disease caused by the yeast *Cryptococcus neojormans.* This organism normally causes no problem in immunocompe-tent people, but it can be devastating to the immunocompromised patient. The incidence of cryptococcosis has increased dramatically during the past decade, primarily because of the AIDS epidemic; it is the most common life-threatening fungal infection in these patients. The disease has a worldwide distribution because of its association with the pigeon (with the organism living in the deposits of excreta left by the birds). Unlike many other pathogenic fungi, *C. neoformans* grows as a yeast both in the soil and in infected tissue. The organism usually produces a prominent mucopolysaccharide capsule that appears to protect it from host immune defenses.

The disease is acquired by inhalation of C. *neoformans* spores into the lungs, resulting in an immediate influx of neutrophils that destroy most of the yeasts. Macrophages soon follow, although resolution of infection in the immunocompctent host ultimately depends on an intact cell-mediated immune system.

Clinical Features

Primary cryptococcal infection of the lungs is often asymptomatic; however, a mild flulike illness may develop. Patients complain of productive cough, chest pain, fever, and malaise. Most patients with a diagnosis of cryptococcosis have a significant underlying medical problem related to immune suppression (e.g., systemic corticosteroid therapy, cancer chemotherapy, malignancy, AIDS). It is estimated that 5% to 10% of AIDS patients acquire this infection.

Dissemination of the infection is common in these immunocompromised patients, and the most frequent site of involvemenl is the meninges, followed by skin, bone, and the prostate gland,

Cryptococcal meningitis is characterized by headache, fever, vomiling, and neck stiffness. In many instances, this is the initial sign of the disease.

Cutaneous lesions develop in 10% to 20% of patients with disseminated disease. These are of particular importance to the clinician because the skin of the head and neck is often involved. The lesions appear as erythematous papules or pustules that may ulcerate, discharging a puslikc material rich in cryptococcal organisms.

Although oral lesions are relatively rare, they have been described as craterlike, nonhealing ulcers that are tender on palpation. Dissemination to salivary gland tissue also has been reported rarely.

Histopathologic Features

Microscopic sections of a cryptococcal lesion generally show a granulomatous inflammatory response to the organism. The extent of the response may vary, however, depending on the host's immune status and the strain of the organism. The yeast appears as a round-to-ovoid structure, 4 to 6 μm in diameter, surrounded by a clear halo that represents the capsule. Staining with the PAS or Grocott-Gomori methenamine silver method can readily identify the fungus; moreover, a mucicarmine stain uniquely demonstrates its mucopolysaccharide capsule.

Diagnosis

The diagnosis of cryptococcosis can be made by several methods, including biopsyand culture. Detection of cryptococcal antigen in the serum or cerebrospinal fluid is also useful as a diagnostic procedure.

Treatment and Prognosis

Management of cryptococcal infections can be very difficult because most of the affected patients have an underlying medical problem. Before amphotcricin B was developed, cryptococcosis was almost uniformly fatal. A combination of systemic amphotericin B and another antifungal drug (flucytosine) is used in most cases to treat this disease. The triazolcs fluconazole and itraconazole have been effective in controlling cryptococcosis, and fluconazole has been approved for this purpose. These drugs produce far fewer side effects than do amphotericin B and flucytosine, and they should prove useful in the future.

ZYGOMYCOSIS (MUCORMYCOSIS; PHYCOMYCOSIS)

Zygomycosis is an opportunistic, frequently fulminant, fungal infection that is caused by normally saprobic organisms of the class Zygomycctcs, including such genera as *Absidia, Mucor, Rhizomucor,* and *Rhizopus.* These organisms are found throughout the world, growing in their natural state on a variety of decaying organic materials. Numerous spores may be liberated into the air and inhaled by the human host.

Zygomycosis may involve any one of several areas of the body, but the rhinoccrebral form is most relevant to the oral health care provider. Zygomycosis is noted especially in insulin-dependent diabetics who have uncontrolled diabetes and are ketoacidotic; however, as with many other fungal diseases, this infection affects immunocompromised patients as well. Only rarely has zygomycosis been reported in apparently healthy individuals.

Clinical and Radiographic Features

The presenting symptoms of rhinocerebral zygomycosis may be exhibited in several ways. Patients may experience nasal obstruction, bloody nasal discharge, facial pain or headache, facial swelling or ccllulitis, and visual disturbances with concurrent proptosis. Symptoms related to cranial nerve involvement (e.g.. facial paralysis) are often present. With progression of disease into the cranial vault, blindness, lethargy, and seizures may develop, followed by death.

If the maxillary sinus is involved, the initial presentation may be seen as intraoral swelling of the maxillary alveolar process, the palate, or both. If the condition remains untreated, palatal ulceration may evolve, with the surface of the ulcer typically appearing black and necrotic. Massive tissue destruction may result if the condition is not treated.

Radiographically, opacification of the sinuses may be observed in conjunction with patchy effacement of the bony walls of the sinuses. Such a picture may be difficult to distinguish from that of a malignancy affecting the sinus area.

Histopathologtc Features

Histopathologic examination of lesional tissue shows extensive necrosis with numerous large (6 to 30 μm in diameter), branching, nonseptate hyphae at the periphery. The hyphae tend to branch at 90-degree angles. The extensive tissue destruction and necrosis associated with this disease are undoubtedly attributable to the preference of the fungi for invasion of small blood vessels. This disrupts normal blood flow to the tissue, resulting in infarction and necrosis. A neutrophilic infiltrate usually predominates in the viable tissue, but the host inflammatory cell response to the infection may be minimal, particularly if the patient is immunosuppressed.

Diagnosis

Diagnosis of zygomycosis is usually based on the histopathologic findings. Because of the grave nature of this infection, appropriate therapy must be instituted in a timely manner (often without the benefit of definitive culture results).

Treatment and Prognosis

Treatment of zygomycosis consists of radical surgical debridement of the infected, necrotic tissue and systemic administration of high doses of amphotericin B, Magnetic resonance imaging of the head is useful in determining the extent of disease involvement so that surgical margins can be planned. In addition, control of the patient's underlying disease (e.g., diabetic ketoacidosis) must be attempted. Despite such therapy, the prognosis is usually poor. Should the patient survive, the massive tissue destruction that remains presents a challenge both functionally and aesthetically. Prosthetic obturation of palatal defects may be necessary.

ASPERQLLOSIS

Aspergtllosis is a fungal disease that is characterized by noninvasive and invasive forms. Noninvasive aspergillosis usually affects a normal host, appearing either as an allergic reaction or a cluster of fungal hyphae. Localized invasive infection of damaged tissue may be seen in a normal host, but a more extensive invasive infection is often evident in the immunocompromised patient. With the advent of intensive chemothcrapeutic regimens, the AIDS epidemic, and both solid-organ and bone marrow transplantation, the prevalence of invasive aspergillosis has increased dramatically in the past 20 years. Patients with uncontrolled diabetes mcllitus are also susceptible to *Aspergiltus* infections. Rarely, invasive aspergillosis has been reported to affect the paranasal sinuses of apparently normal immunocompetent individuals.

Normally, the various species of the *Aspergillus* genus reside worldwide as saprobic organisms in soil, water, or decaying organic debris. Resistant spores are released into the air and inhaled by the human host, resulting in opportunistic fungal infection second in frequency only to candidiasis. Interestingly, most species of *Aspergillus* cannot grow at 37° C; only the pathogenic species have the ability to replicate at body temperature.

The two most commonly encountered species of *Aspergillus* in the medical setting arc A. *flavus* and *A. fumigatus,* with *A. fumigatus* being responsible for 90% of the cases of aspergillosis. The patient may acquire such infections in the hospital ("nosocomial" infection), especially if remodeling or building construction is being performed in the immediate area. Such activity often stirs up the spores, which are then inhaled by the patient.

Clinical Features

The clinical manifestations of aspergillosis vary, depending on the host immune status and the presence or absence of tissue damage. In the normal host, the disease may appear as an allergy affecting either the sinuses (allergic fungal sinusitis) or the bronchopulmonary tract. An asthma attack may be triggered by inhalation of spores by a susceptible person. Sometimes a low-grade infection becomes established in the maxillary sinus, resulting in a mass of fungal hyphae called an aspergilloma. Occasionally, the mass will undergo dystrophic calcification, producinga radiopaque body called an antrolith within the sinus.

Another presentation that may be encountered by the oral health care provider is aspergillosis after tooth extraction or endodontic treatment, especially in the maxillary posterior segments. Presumably, tissue damage predisposes the sinus to infection, resulting in symptoms of localized pain and tenderness accompanied by nasal discharge. Immunocompromised patients a re particularly susceptible to oral aspergillosis, and some investigators have suggested that the portal of entry may be the marginal gingiva and gingival sulcus. Painful gingival ulcera-tions arc initially noted, and peripherally the mucosa and soft tissue develops diffuse swelling with a gray or viola-ceous hue. If the disease is not treated, extensive necrosis, seen clinically as a yellow or black ulcer, and facial swelling evolve.

Disseminated aspergillosis occurs principally in immunocompromised patients, particularly in those who have leukemia or who are taking high daily doses of cor-ticosteroids. Such patients usually exhibit symptoms related to the primary site of inoculation: the lungs. The patient typically has chest pain, cough, and fever, but such symptoms are vague. Therefore, obtaining an early, accurate diagnosis may be difficult. Once the fungal organism obtains access to the blood stream, infection can spread to such sites as the CNS, eye, skin, liver, gastrointestinal tract, bone, and thyroid gland.

Histopathologic Features

Tissue sections of *Aspergillus* lesions show varying numbers of branching, septate hyphae, 3 to 4 μm in diameter. These hyphae show a tendency to branch at an acute angle and to invade adjacent small blood vessels. Occlusion of the vessels often results in the characteristic pattern of necrosis associated with this disease. In the immunocompetenr host, a granulomatous inflammatory

response in addition to necrosis can be expected. In the immunocompromised patient, however, the inflammatory response is often weak or absent, leading to extensive tissue destruction.

Diagnosis

Although the diagnosis of fungal infection can be established by identification of hyphae within tissue sections, this finding is only suggestive of aspergillosis because other fungal organisms may appear similar microscopically. Ideally, the diagnosis should be supported by culture of the organism from the lesion; however, from a practical standpoint, treatment may need to be initiated immediately to prevent the patient's demise. Culture specimens of sputum and blood arc of limited value because they are often negative despite disseminated disease.

Treatment and Prognosis

Treatment depends on the clinical presentation of aspergillosis. For immunocompetent patients with a non-invasive aspergilloma, surgical debridement may be all that is necessary. Patients who have allergic fungal sinusitis are treated with debridement and corticosteroids. For localized invasive aspergillosis in the immunocompetent host, debridement is indicated. This may be combined with either itraconazole or systemic amphotericin B therapy, depending on the severity of the infection. Itraconazole is preferred if the patient can take oral medication, has reasonable gastrointestinal function, and is not taking any other medications that contraindicate the use of itraconazole. Immunocompromised patients who have invasive aspergillosis should be treated by aggressive debridcment of necrotic tissue, combined with systemic antifungal therapy as described previously.

The prognosis for immunocompromised patients is much worse compared with immunocompetent individuals, particularly if the infection is disseminated. Even with appropriate therapy, only about one third of these patients survive. Because aspergillosis in the immunocompromised patient usually develops while the individual is hospitalized, particular attention should be given to the ventilation system in the hospital to prevent patient exposure to the airborne spores of *Aspergillus.*

TOXOPLASMOSIS

Toxoplasmosis is a relatively common disease caused by the obligate intracclular protozoal organism *Toxoptasma gondii.* For normal, healthy adults, the organism poses no problems, and 20% to 30% of adults in the United States may have had asymptomatic infection. Unfortunately, the disease can be devastating for the developing fetus or the immunocompromised patient. Other mammals, particularly members of the cat family, are vulnerable to infection, and cats are considered to be the definitive host. T. *gondii* multiplies in the intestinal tract of the cat by means of a sexual life cycle, discharging numerous oocysts in the cat feces. These oocysts can then be ingested by another animal or human, resulting in the production of disease.

Clinical Features

In the normal, immunocompetent individual, infection with T. *gondii* is often asymptomatic. If symptoms develop, they are usually mild and resemble infectious mononucleosis; patients may have a low-grade fever, cervical lymphadenopathy, fatigue, and muscle or joint pain. These symptoms may last from a few weeks to a few months, although the host typically recovers without therapy. Sometimes the lymphadenopathy involves one or more of the lymph nodes in the paraoral region, such as the buccal lymph node. In such instances, the oral health care provider may discover the disease.

In immunosuppressed patients, toxoplasmosis may represent a new, primary infection or reactivation of previously encysted organisms. The principal groups at risk include the following:

- AIDS patients
- Transplant recipients
- Cancer patients

Manifestations of infection can include necrotizing encephalitis, pneumonia, and myositis or myocarditis. In the United States, it is estimated that from 3% to 10% of AIDS patients will experience CNS involvement. CNS infection is very serious. Clinically, the patient may complain of headache, lethargy, disorientation, and hcmiparesis.

Congenital toxoplasmosis occurs when a nonimmune mother contracts the disease during her pregnancy and the organism crosses the placental barrier, infecting the developing fetus. The potential effects of blindness, mental retardation, and delayed psychomotor development are most severe if the infection occurs during the first trimester of pregnancy.

Histopathologic Features

Histopathologic examination of a lymph node obtained from a patient with active toxoplasmosis shows characteristic reactive germinal centers exhibiting an accumulation of cosinophilic macrophages. The macrophagcs encroach on the germinal centers and accumulate within the subcapsular and sinusoidal regions of the node.

Diagnosis

The diagnosis of toxoplasmosis is usually established by identification of rising serum antibody liters to T. *gondii* within 10 to 14 days after infection. Immunocompromised patients, however, may not be able to generate an antibody response; therefore, the diagnosis may rest on the clinical findings and the response of the patient to therapy.

Biopsy of an involved lymph node may suggest the diagnosis; however, the diagnosis should be confirmed by scrologic studies, if possible.

Treatment and Prognosis

Most healthy adults with toxoplasmosis require no specific treatment because of the mild symptoms and self-limiting course. Perhaps more importantly, pregnant women should avoid situations that place them at risk for the disease. Handling or eating raw meat or cleaning a cat litter box should be avoided until after delivery. If exposure during pregnancy is suspected, treatment with a combination of sulfadiazine and pyrimethamine often prevents transmission of T. *gondii* to the fetus. Because these drugs act by inhibiting folate metabolism of the protozoan, folinic acid is given concurrently to help prevent hematologic complications in the patient. A similar drug regimen is used to treat immunosuppressed individuals with toxoplasmosis, although clindamycin may be substituted for sulfadiazine in managing patients who are allergic to suite drugs. Because most cases of toxoplasmosis in AIDS patients represent reactivation of encysted organisms, prophylactic administration of trimethoprim and sulfamethoxazole is generally recommended.

LECTURE 5

BACTERIAL INFECTIONS. ULCERATIVE-NECROTIC DAMAGES OF ORAL MUCOSA.
ORAL MANIFESTATIONS OF TUBERCULOSIS AND SEXUALLY TRANSMITTED DISEASES. CLINIC, DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, DENTIST'S TACTICS. AIDS.

Acute Necrotizing Ulcerative Gingivitis (ANUG)

The term ***acute necrotizing ulcerative gingivitis*** (ANUG) denotes an inflammatory destructive disease of the gingiva which presents characteristic signs and symptoms. Other terms by which this condition is known are Vincent's infection, acute ulceromembranous gingivitis, trench mouth, trench gums, phagedenic gingivitis, acute ulcerous gingivitis, acute ulcerative gingivitis,

ulcerative gingivitis, ulcerative stomatitis, Vincent's stomatitis, Plaut-Vincent's stomatitis, stomatitis ulcerosa, stomatitis ulcero-membranacea, fusospirillary gingivitis, fusospirillary marginal gingivitis.

Acute necrotizing ulcerative gingivitis (ANUG, Vincent's infection, trench mouth) has several possible secondary etiologic factors. Stress and anxiety are probably significant contributing factors, leading to the lowered resistance of the body. ANUG occurs in young persons, in the case of pre-existing simple gingivitis and poor oral hygiene.

Clinical features

Necrotizing ulcerative gingivitis most often occurs as an acute disease. Its relatively mild and more persistent form is referred to as ***subacute***. Recurrent disease is marked by periods of remission and exacerbation. Reference is sometimes made to ***chronic*** necrotizing ulcerative gingivitis. However, it is difficult to justify this designation as a separate entity because most periodontal pockets with ulceration and destruction of gingival tissue present comparable microscopic and clinical features.

Acute necrotizing ulcerative gingivitis is characterized by sudden onset, frequently following an episode of debilitating disease or acute respiratory infection. Occasionally, patients report that it appeared shortly after they had their teeth cleaned. Change in living habits, protracted work without adequate rest, and psychological stress are frequent features of the patient's history.

Characteristic lesions are punched-out, crater-like depressions at the crest of the gingiva that involve the interdental papillae, the marginal gingiva, or both (fig.14). The surface of the gingival craters is covered by a gray, pseudomembranous slough demarcated from the remainder of the gingival mucosa by a pronounced linear erythaema. In some instances, the lesions are denuded of the surface pseudomembrane, exposing the gingival margin, which is red, shiny, and hemorrhagic. The characteristic lesions progressively destroy the gingiva and underlying periodontal tissues.

A fetid odor, increased salivation, and spontaneous gingival hemorrhage or pronounced bleeding upon the slightest stimulation are additional characteristic clinical signs.

The lesions are extremely sensitive to touch, and the patient complains of a constant radiating, gnawing pain that is intensified by spicy or hot foods and mastication. There is a metallic foul taste and the patient is conscious of an excessive amount of „pasty" saliva. The teeth are characteristically described as feeling like "wooden pegs."

Acute necrotizing ulcerative gingivitis occurs in otherwise disease-free mouths or superimposed upon chronic gingivitis or periodontal pockets. Involvement may be limited to a single tooth or group of teeth, or be widespread throughout the mouth. It is rare in edentulous mouths, but isolated spherical lesions occasionally occur on the soft palate.

Patients are usually ambulatory, with a minimum of systemic complications. Local lymphadenopathy and slight elevation in temperature are common features of the mild and moderate stages of the disease. In severe cases there are marked systemic complications such as high fever, increased pulse rate, leukocytosis, loss of appetite, and general lassitude. Systemic reactions are more severe in children. Insomnia, constipation, gastrointestinal disorders, headache, and mental depression sometimes accompany the condition.

In very rare cases severe sequelae such as the following may occur: noma or gangrenous stomatitis, fusospirochetal meningitis and peritonitis, pulmonary infections, toxemia, and fatal brain abscess.

The clinical course is indefinite. If untreated, it may result in progressive destruction of the periodontium and denudation of the roots, accompanied by an increase in the severity of toxic systemic complications. It often undergoes a diminution in severity leading to a subacute stage with varying degrees of clinical symptomatology. The disease may subside spontaneously without treatment. Such patients generally present a history of repeated remissions and exacerbations. Recurrence of the condition in previously treated patients is also frequent.

Microscopically, the lesion appears as a nonspecific acute, necrotizing inflammation at the gingival margin involving both the stratified squamous epithelium and the underlying connective tissue. The surface epithelium is destroyed and replaced by a pseudomembranous meshwork of fibrin, necrotic epithelial cells, polymorphonuclear leukocytes, and various types of

microorganisms. This is the zone that appears clinically as the surface pseudomembrane. The underlying connective tissue is markedly hyperemic with numerous engorged capillaries and a dense infiltration of polymorphonuclear leukocytes. This acutely inflamed hyperemic zone appears clinically as the linear erythaema beneath the surface pseudomembrane.

The relation of bacteria to the characteristic lesion has been studied with the light microscope and electron microscope. With the former it appears that the exudate on the surface of the necrotic lesion contains microorganisms which morphologically resemble cocci, fusiform bacilli, and spirochetes. The layer between necrotic and living tissue contains enormous numbers of fusiform bacilli and spirochetes in addition to leukocytes and fibrin. Spirochetes invade the underlying living tissue; other organisms seen on the surface are not found there. Some investigators feel that the spirochetes are pushed into the tissue when gingival specimens are removed for microscopic study.

Treatment of Acute Necrotizing Ulcerative Gingivitis (ANUG)

The treatment of ANUG has to be complex etiotropic, pathogenic, symptomatic. It must be also local and general.

Process in the gums can be compared with the course of the wound healing in general surgery where two phases can be distinguished: ***hydratation and dehydratation with epithelization***.

In the phase of ***hydratation*** the surgical processing of the ulcerations and necrotic tissues is of great importance. It is carried out under the local applicational or infiltrational anaesthesia. For applicational anaesthesia Solution of 1% dicaini, 1% Solution of Mefeminatum Na, 4-5% Solution of propolis, 0,5-1% Novocaini or 10% Lidocaini spray (it has an irritable effect on the inflammed gums) are used.

After the anaesthesia removal of plaque and calculus is necessary. It has to be followed by antiseptic irrigations. In this case broad-spectrum antiseptics, active to gram+ and gram- microorganisms are recommended. Among them 0,2% solution of Chlorhexidinum bigluconatis, derivatives of nitrofuran: Solution of Furacilinum (1:5000). Solution of Furaginum (1:13000). Than mechanical debridment of necrotic tissues and debris is carried out (with the help of excavator). Caries cavities have to be treated with a strong antiseptic solution and temporary filled.

To improve the effect of mechanical debridment proteolytic enzymes (trypsini, chimotrypsini, terrylitini) are used. 1 mg of proteolytic enzyme is dissolved in 1 ml of one of the solutions – 0,5% novocaini, isotonic solution of NaCl, 0,2% Solution of Chlorhexydinum Bigluconatis, solution of antibiotics (streptomycin, morphocyclin, lincomycin). Metronidazolum (in the forms of solutions and ointments), and also metronidazolum with chlorhexidine 0,2% are especially effective in the treatment of ANUG. Proteolytic enzymes can be dissolved in glycerinum or tocopherol acetatum (vit. E) (1 mg to 1 ml), but in this case their penetration into the gums will be delayed. Applications including enzymes, antibacterial medications sometimes can be connected with Dymetyl-Sulfoxidum which increases gums permeability. Applications are fixed on the gums for 10-15 minutes.

Applications of above-mentioned medications can be followed by oxygenotherapy, that is a simultaneous application of cotton rolls impregnated with KMnO4 1:10000 and 3% solution of H_2O_2. They produce intensive oxygen secretion and inactivate anaerobic microorganisms. These applications are made 2-3 times in succession.

Local treatment in the hydratation period of ANUG is connected with a general treatment. Especially general treatment is necessary in moderate and heavy stages of the disease, when the process spreads to more that 5-6 regions of the dentition.

General therapy includes desintoxication remedies: Solution of Natrii thiosulfas (Rp.; Natrii thiosulfatis 10,0 Aq. destill. 100 ml, M.D.S. 1-2 tablespoons 3 times a day), lot of natural juices, water with lemon; antihistamine medications; vitamin therapy (especially vit. C., A, B); not-irritative food reach in fruits and vegetables.

Antibacterial therapy includes metronidazol (0,25g 3 times a day within 5-7 days) or lincomicyn (0,25-0,5g 3 times a day 2 hours before or after the meal, rondomicyn (0,3g 2-3 times a day after the meal).

In the phase of ***dehytratation*** (which started in 3-5 days after the hydratation stage of ANUG) medications stimulating regeneration are very important. Among them locally (in the forms of applications and as the part of periodontal dressings) are used: vit. A, E and their combination, natural oils – Oleum Hippopheal, Oleum Rosae. Remedies stimulating metabolic processes are effective in this phase of treatment (5-10% ointment of Methyluracilum), biogenic stimulators: juices of Colanchoe, Aloe (Extractum Aloes fluidum, linimentum Aloe), Biossedum, Solcoseryl ointment, ointment "Propoceum" (includes 10% extract of propolis), aerolosolum "Proposolum", synthetic balms Vinilin, Vinizol.

Medications which are produced from the cattle cartilages and belong to the group of acid mucopolysaccharids with antiinflammatory and stimulating regeneration properties - Chonsuridum, Luronidum.

Rp.: Chonsuridi 0,1

D.t.d. N 6

S. For gums application. Before treatment dissolve 1 amp. in 10 ml of 0,5% Novocainum or isotonic solutions.

Vincent angina: This is trench mouth, a progressive painful infection with ulceration, swelling and sloughing off of dead tissue from the mouth and throat due to the spread of infection from the gums. Certain germs (including fusiform bacteria and spirochetes) are thought to be involved. Vincent's angina is best treated with the antibiotic penicillin.

This condition is also called Vincent (or Vincent's) angina after the French physician Henri Vincent (1862-1950). The word "angina" comes from the Latin "angere" meaning "to choke or throttle."

As with most poorly understood diseases, Vincent angina goes by many other names including acute necrotizing ulcerative gingivitis (ANUG), acute membranous gingivitis, fusospirillary gingivitis, fusospirillosis, fusospirochetal gingivitis, necrotizing gingivitis, phagedenic gingivitis, ulcerative gingivitis, Vincent stomatitis, Vincent gingivitis, and Vincent infection.

Noma

Noma, or gangrenous stomatitis, is a rare rapidly progressive,opportunistic infection involving the oral tissues.

Etiology *Fusobacterium nucleatum*, *Prevotella intermedia*, *Borrelia vincentii*, *Streptococcus* species, and *Staphylococcus aureus* are the main pathogenic microorganisms. Predisposing factors are poor oral hygiene, severe protein malnutrition, severe diabetes mellitus, leukemias, and other malignancies and immune defects.

Noma usually begins as necrotizing ulcerative gingivitis that quickly spreads to the adjacent soft tissue forming abnormal necrotizing ulcerations. The gangrenous necrosis progressively involves the buccae, the lips, and the adjacent bone, producing catastrophic lesions on the face. The ulcers are covered with whitish-yellowor brown fibrin and debris. Salivation, halitosis, fever, malaise, and regional lymphadenopathy are common. The diagnosis is usually based on the history and the clinical features.

Differential diagnosis Malignant granuloma, tuberculosis, agranulocytosis,leukemias.

Treatment Appropriate antibiotics, and conservative debridement of the lesion.

SYPHILIS (LUES)

Syphilis is a worldwide chronic infection produced by *Treponema pallidum*. The organism is extremely vulnerable to drying; therefore, the primary modes of transmission are sexual contact or from mother to fetus. Although the risk of infection from blood transfusion is negligible because of serologic testing of donors, transmission through exposure to infected blood is theoretically possible because the organism may survive up to 5 days in refrigerated blood.

After the advent of penicillin therapy in the 1940s, the incidence of syphilis slowly decreased to a low point in 1956; since that time, the infection rate has peaked and troughed in approximately 10-year cycles. Overall, there is a trend toward an increasing incidence. The World Health Organization estimated approximately 12 million new cases of syphilis occurred in adults worldwide in 1995. The prevalence of infection is 50 to 100 times higher in the United States when compared with other industrialized countries.

The primary cause for a recent upsurge in cases appears related to crack cocaine abuse and the barter of illegal drugs for sex. Although the data varies from year to year, a significant and prolonged increased prevalence has been seen in African Americans. In the past, there was a male predominance that approached 3.5:1 during certain recording periods. Recently the male-to-female ratio has dropped to approximately 1:1, most likely because of elevated rates of syphilis among women involved in prostitution related to crack cocaine. This increased incidence in females has ultimately resulted in another increasing problem, congenital syphilis.

In patients with syphilis, the infection undergoes a characteristic evolution that classically proceeds through three stages. A syphilitic patient is highly infectious only during the first two stages, but pregnant women also may transmit the infection during the latent stage. Maternal transmission during the first two stages of infection almost always results in miscarriage, stillbirth, or an infant with congenital malformations. The longer the mother has had the infection, the less the chance of fetal infection. Infection of the fetus may occur at any time during pregnancy, but the stigmata do not begin to develop until after the fourth month of gestation. The clinical changes secondary to the fetal infection are known as *congenital syphilis*. Because of the morbidity and mortality associated with this infection, it is recommended that all pregnant women be screened for syphilis early in the gestation period.

Oral syphilitic lesions are uncommon but may occur in any stage. Many of the changes are secondary to obliterative endarteritis, which occurs in areas of infection.

Clinical Features

Primary syphilis. Primary syphilis is characterized by the chancre that develops at the site of inoculation, becoming clinically evident 3 to 90 days after the initial exposure. Although multiple lesions may be seen occasionally, the majority of chancres are solitary. The external genitalia and anus are the most common sites, and the affected area begins as a papular lesion, which develops a central ulceration. Less than 2% of chancres occur in other locations, but the oral cavity is the most common extragenital site. Oral lesions are seen most commonly on the lip, but other sites include the tongue, palate, gingiva, and tonsils. The oral lesion appears as a painless, clean-based ulceration or, rarely, as a vascular proliferation resembling a pyogenic granuloma. Regional lymphadenopathy, which may be bilateral, is seen in most patients. At this time the organism is spreading systemically through the lymphatic channels, setting the stage for future progression. If untreated, the initial lesion heals within 3 to 8 weeks.

Secondary syphilis. The next stage is known as secondary (disseminated) syphilis and is discovered clinically 4 to 10 weeks after the initial infection. The lesions of secondary syphilis may arise before the primary lesion has resolved completely. During secondary syphilis, systemic symptoms often arise. The most common are painless lymphadenopathy, sore throat, malaise, headache, weight loss, fever, and musculoskeletal pain. A consistent sign is a diffuse, painless, maculopapular cutaneous rash, which is widespread and can even affect the palmar and plantar areas. The rash also may involve the oral cavity and appear as red, maculopapular areas. Although the skin rash may result in areas of scarring and hyperpigmentation or hypopigmentation, it heals without scarring in the vast majority of patients.

In addition, roughly 30% of patients have focal areas of intense exocytosis and spongiosis of the oral mucosa, leading to zones of sensitive whitish mucosa known as mucous patches. Subsequently, superficial epithelial necrosis may occur, leading to sloughing and exposure of the underlying raw connective tissue. These may appear on any mucosal surface but are found commonly on the tongue, lip, buccal mucosa, and palate. Occasionally, papillary lesions that resemble viral papillomas may arise during this time and are known as *condylomata lata*. In contrast to the isolated chancre noted in the primary stage, multiple lesions are typical of secondary syphilis. Spontaneous resolution usually occurs within 3 to 12 weeks; however, relapses may occur during the next year.

On occasion, especially in the presence of a compromised immune system, secondary syphilis can exhibit an explosive and widespread form known as *lues maligna***.** This form has prodromal symptoms of fever, headache, and myalgia, followed by the formation of necrotic ulcerations, which commonly involve the face and scalp. Oral lesions are present in more than 30% of affected patients. Malaise, pain, and arthralgia are seen occasionally. Several cases of lues maligna have been reported in patients with acquired immunodeficiency syndrome (AIDS), and this possibility should be kept in mind whenever human immunodeficiency virus (HIV) infected patients have atypical ulcerations of the skin or oral mucosa.

Tertiary syphilis. After the second stage, patients enter a period in which they are free of lesions and symptoms, known as *latent syphilis*. This period of latency may last from 1 to 30 years; then (in approximately 30% of patients) the third stage, which is known as tertiary syphilis, develops. The third stage of syphilis includes the most serious of all complications. The vascular system can be affected significantly through the effects of the earlier arteritis. Aneurysm of the ascending aorta, left ventricular hypertrophy, and congestive heart failure may occur. Involvement of the central nervous system may result in tabes dorsalis, psychosis, dementia, paresis, and death. Less significant, but more characteristic, are scattered foci of granulomatous inflammation, which may affect the skin, mucosa, soft tissue, bones, and internal organs. This active site of granulomatous inflammation, known as a ***gumma***, appears as an indurated, nodular, or ulcerated lesion that may produce extensive tissue destruction. Intraoral lesions usually affect the palate or tongue. When the palate is involved, the ulceration frequently perforates through to the nasal cavity. The tongue may be involved diffusely with gummata and appear large, lobulated, and irregularly shaped. This lobulated pattern is termed *interstitial glossitis* and is thought to be the result of contracture of the lingual musculature after healing of gummas. Diffuse atrophy and loss of the dorsal tongue papillae produce a condition called *luetic glossitis*. In the past, this form of atrophic glossitis was thought to be precancerous, but several more recent publications dispute this concept.

Congenital syphilis. In 1858, Sir Jonathan Hutchinson described the changes found in congenital syphilis and defined the following three pathognomonic diagnostic features, known as ***Hutchinson's triad:***

- Hutchinson's teeth
- Ocular interstitial keratitis
- Eighth nerve deafness

Like many diagnostic triads, few patients exhibit all three features.

The infection alters the formation of both the anterior teeth (***Hutchinson's incisors***) and the posterior dentition (*mulberry molars, Fournier's molars, Moon's molars*). Hutchinson's incisors exhibit their greatest mesiodistal width in the middle third of the crown. The incisal third tapers to the incisal edge, and the resulting tooth resembles a straightedge screwdriver. The incisal edge often exhibits a central hypoplastic notch. Mulberry molars taper toward the occlusal surface with a constricted grinding surface. The occlusal anatomy is abnormal, with numerous disorganized globular projections that resemble the surface of a mulberry.

Interstitial keratitis of the eyes is not present at birth but usually develops between the ages of 5 and 25 years. The affected eye has an opacified corneal surface, with a resultant loss of vision. In addition to Hutchinson's triad, a number of other alterations may be seen.

Histopathologic Features

The histopathologic picture of the oral lesions in the syphilitic patient is not specific. During the first two stages, the pattern is similar. The surface epithelium is ulcerated in primary lesions and may be ulcerated or hyperplastic in the secondary stage. The underlying lamina propria may demonstrate an increase in the number of vascular channels, and an intense chronic inflammatory reaction is present. The infiltrate is composed predominantly of lymphocytes and plasma cells and often demonstrates a perivascular pattern. Although the presence of plasma cells within the infiltrate may suggest the diagnosis of syphilis on the skin, their presence in areas of oral ulceration is commonplace and, therefore, not necessarily of diagnostic significance. The use of special silver impregnation techniques, such as Warthin-Starry or Steiner stains, often shows scattered corkscrew-like spirochetal organisms. In addition, the organism can be detected in tissue through direct fluorescent antibody testing.

Oral tertiary lesions typically exhibit surface ulceration, with peripheral pseudoepitheliomatous hyperplasia. The underlying inflammatory infiltrate usually demonstrates foci of granulomatous inflammation with well-circumscribed collections of histiocytes and multinucleated giant cells. Even with special stains, the organisms are hard to demonstrate in the third stage, and the inflammatory response is thought to be an immune reaction rather than a direct response to T. *paliidum.*

Diagnosis

The diagnosis of syphilis is best confirmed by demonstrating the spiral organism by dark-field examination of a smear of the exudate of an active lesion. False-positive results are possible in the oral cavity because of morphologically similar oral inhabitants, such as T. *microdentium, T. macrodentium,* and T. *mucosum.* Demonstration of the organism on a smear or in biopsy material should be confirmed through the use of specific immunofluorescent antibody or serologic tests.

Several nonspecific and not highly sensitive serologic screening tests for syphilis are available. These include the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR). After the first 3 weeks of infection, the screening tests are positive strongly throughout the first two stages. After the development of latency, the positivity generally subsides with time.

Specific and highly sensitive serologic tests for syphilis are also available. These include the fluorescent treponemal antibody absorption (FTA-ABS) and T. *pallidum* hemagglutination assays (TPHA). These tests become positive at the time of the development of the first lesion of primary syphilis and remain positive for life. This lifelong persistence of positivity limits their usefulness in the diagnosis of a second incidence of infection. In cases of suspected reinfection, therefore, the organisms should be demonstrated within the tissue or exudates.

Treatment and Prognosis

The treatment for syphilis necessitates an individual evaluation and a customized therapeutic approach. The treatment of choice is penicillin. The dose and administration schedules vary according to the stage, neurologic involvement, and immune status. Most patients obtain a clinical cure with penicillin, but it must be remembered that T. *pallidum* can escape the lethal effects of the antibiotic when the organism is located within the confines of lymph nodes or the central nervous system. Therefore, antibiotic therapy may not always result in a total cure in patients with neurologic involvement but may arrest only the clinical presentations of the infection. Patients with immunosuppression, such as those with AIDS, may not respond appropriately to standard antibiotic regimens, and numerous reports have documented a continuation to neurosyphilis despite seemingly appropriate single-dose therapy. Erythromycin or tetracycline is given to patients who are allergic to penicillin.

GONORRHEA

Gonorrhea, a sexually transmitted disease that is produced by *Neisseria gonorrhoeae,* represents the most common reportable bacterial infection in the United States. The disease is epidemic, especially in urban areas, and millions of people are infected each year. Although the prevalence of gonorrhea has been declining since a peak in 1975, the rate in the United States remains the highest of any industrialized country. The incidence of gonorrhea between 1981 and 1996 has decreased

71.3%; however, certain segments of the population remain at high risk. Groups exhibiting an increased prevalence of infection include those with a low socio-economic or education level, injecting drug users, prostitutes, homosexual men, and military personnel.

Clinical Features

The infection is spread through sexual contact, and most lesions occur in the genital areas. Indirect infection is rare because the organism is sensitive to drying and cannot penetrate intact stratified squamous epithelium. The incubation period is typically 2 to 5 days. Affected areas often demonstrate significant purulent discharge, but approximately 10% of men and up to 50% of women who contract gonorrhea are asymptomatic.

In men, the most frequent site of infection is the urethra, resulting in purulent discharge and dysuria. Less common primary sites include the anorectal and pharyngeal areas. The cervix is the primary site of involvement in women, and the chief complaints are increased vaginal discharge, intermenstrual bleeding, genital itching, and dysuria. The organism may ascend to involve the uterus and ovarian tubes, leading to the most important female complication of gonorrhea—pelvic inflammatory disease (PID). The symptoms of PID include cramps and abnormal bleeding, and they may be severe or mild. The long-term complications of PID include ectopic pregnancies or infertility from tubal obstruction.

Between 0.5% and 3.0% of untreated patients with gonorrhea will have disseminated gonococcal infections from systemic bacteremia. The most common signs of dissemination are myalgia, arthralgia, polyarthritis, and dermatitis. In 75% of patients with disseminated disease, a characteristic skin rash develops. The dermatologic lesions consist of discrete papules and pustules that often exhibit a hemorrhagic component and occur primarily on the extremities. Less common alterations secondary to gonococcal septicemia include fever, endocarditis, pericarditis, meningitis, and oral mucosal lesions of the soft palate and oropharynx, which are similar to aphthous ulcerations.

Approximately 20% of patients with gonorrhea will exhibit involvement of the oropharyngeal region. Gonococcal septicemia, kissing, and cunnilingus may transmit the organism to this site, but most cases of oral gonorrhea appear to be a result of fellatio. Therefore, the majority has been reported in women or homosexual men. The most common site of oral involvement is the pharyngeal area alongwith the tonsils and uvula. A mild-to-moderate sore throat often is accompanied by nonspecific, diffuse oropharyngeal erythema. Involved tonsils typically demonstrate edema and erythema, often with scattered, small punctate pustules. Rarely, lesions have been reported in the anterior portion of the oral cavity, with areas of infection appearing erythematous, pustular, erosive, or ulcerated. Submandibular or cervical lymphadenopathy may be present.

During birth, infection of an infant's eyes can occur from an infected mother who may be asymptomatic. This infection is called *gonococcal ophthalmia neonatorum* and can rapidly cause blindness.

Diagnosis

To confirm the diagnosis, a Gram stain of the purulent material can be used to demonstrate gram-negative diplococci within the neutrophils. Confirmation of the diagnosis is made through culture and sugar fermentation tests or by a positive fluorescent antibody test.

Treatment and Prognosis

Patients with gonorrhea are at risk for additional sexually transmitted diseases, most commonly *Chlamydia trachomatis.* Isolation of *Chlamydia* is costly and tends to delay therapy. The most cost-effective approach is to cotreat all cases of gonorrhea for possible associated chlamydial infection; the preferred regimen is ceftriaxone and doxycycline. In patients allergic to cephalosporins, spectinomycin is used instead of ceftriaxone. Rescreening is recommended I to 2 months after therapy. The most common cause for treatment failure is reexposure to infected partners, who often are asymptomatic; therefore, the treatment of all recent sexual partners is recommended.

Prophylactic ophthalmic erythromycin, tetracycline, or silver nitrate is applied to the newborn's eyes to prevent the occurrence of gonococcal ophthalmia neonatorum.

TUBERCULOSIS

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis.* Worldwide, more than I billion people are infected, with 8 million new cases and 3 million deaths per year. In the United States, the disease has been declining since the 1800s, especially since the introduction of effective antimicrobials in the 1940s. The decline ceased abruptly in the early 1980s and appears to be the result of a combination of several factors. The HIV epidemic, increased immigration from countries with endemic tuberculosis, transmission of tuberculosis in crowded or unsanitary environments, and a decline of the health care infrastructure have been implicated in the recent resurgence. Most infections are the result of direct person-to-person spread through airborne droplets from a patient with active disease.

Nontuberculous mycobacterial disease can occur from a variety of organisms. Before the tuberculin testing of dairy herds, many cases arose from the consumption of milk infected with *M. bovis.* Except for HIV-infected individuals, most other cases of nontuberculous mycobacterial disease appear as localized chronic cervical lymphadenitis in otherwise healthy children. In patients with AIDS, *M. civium-intracellulare* is a common cause of opportunistic infections.

Infection must be distinguished from active disease. **Primary tuberculosis** occurs in previously unexposed people and almost always involves the lungs. The organism initially elicits a nonspecific, chronic inflammatory reaction. In most individuals, the primary infection results only in a localized, fibrocalcified nodule at the initial site of involvement. However, viable organisms may be present in these nodules and remain dormant for years to life.

Only about 5% to 10% of patients with tuberculosis progress from infection to active disease, and an existing state of immunosuppression often is responsible. In rare instances, active tuberculosis may ensue directly from the primary infection. However, active disease usually develops later in life from a reactivation of organisms in a previously infected person. This reactivation is typically associated with compromised host defenses and is called **secondary tuberculosis.** Diffuse dissemination through the vascular system may occur and has been termed **miliary tuberculosis.** Secondary tuberculosis often is associated with old age, poverty, and crowded living conditions. AIDS represents one of the strongest known risk factors for progression from infection to disease. The prevalence of active tuberculosis in patients with AIDS is approximately 100 times that documented in the general population.

Clinical and Radiographic Features

Primary tuberculosis is usually asymptomatic. Occasionally, fever and pleural effusion may occur.

Classically, the lesions of secondary tuberculosis are located in the apex of the lungs but may spread to many different sites by expectorated infected material or through the lymphatic or vascular channels. Typically, patients have a low-grade fever, malaise, anorexia, weight loss, and night sweats. With pulmonary progression, a productive cough develops, often with hemoptysis or chest pain. Progressive tuberculosis may lead to a wasting syndrome that, in the past, was termed ***consumption,*** because it appeared that the patient's body was being consumed or destroyed.

Extrapulmonary tuberculosis is seen and represents an increasing proportion of the currently diagnosed cases. In patients with AIDS, greater than 50% will have extrapulmonary lesions. Any organ system may be involved, including the lymphatic system, skin, skeletal system, central nervous system, kidneys, and gastro-intestinal tract. Involvement of the skin may develop and has been called lupus vulgaris.

Head and neck involvement is not rare. The most common extrapulmonary sites in the head and neck are the cervical lymph nodes followed by the larynx and middle ear. Much less common sites include the nasal cavity, nasopharynx, oral cavity, parotid gland, esophagus, and spine.

Oral lesions of tuberculosis are uncommon, with most cases appearing as a chronic painless ulcer. Less frequent presentations include nodular, granular, or (rarely) firm leukoplakic areas. Most of the lesions represent secondary infection from the initial pulmonary lesions. It is unclear whether these develop from hematogenous spread or from exposure to infected sputum. The

reported prevalence of clinically evident oral lesions varies from 0.5% to 1.5%. However, one autopsy study revealed a prevalence of close to 20% when the tongues of those infected were examined microscopically. The discovery of pulmonary tuberculosis as a result of the investigation of oral lesions occurs but is unusual. Primary oral tuberculosis without pulmonary involvement is rare.

When present, primary oral tuberculosis usually involves the gingiva, mucobuccal fold, and areas of inflammation adjacent to teeth or in extraction sites; secondary oral lesions are mostly present on the tongue, palate, and lip. Primary oral lesions are usually associated with enlarged regional lymph nodes. Tuberculous osteomyelitis has been reported in the jaws and appears as ill-defined areas of radiolucency.

Nontuberculous mycobacterial infections from contaminated milk are currently rare in the industrialized world because of pasteurization of milk and rapid elimination of infected cows. Drinking contaminated milk can result in a form of mycobacterial infection known as *scrofula***.** Scrofula exhibits enlargement of the oro-pharyngeal lymphoid tissues and cervical lymph nodes. On occasion, the involved nodes may develop significant caseous necrosis and form numerous fistulas through the overlying skin. In addition, areas of nodal involvement may radiographically appear as calcified lymph nodes. Pulmonary involvement is unusual in patients with scrofula.

Histopathologic Features

The cell-mediated hypersensitivity reaction is responsible for the classic histopathologic presentation of tuberculosis. Areas of infection demonstrate the formation ofgranulomas, which are circumscribed collections ofepithelioid histiocytes, lymphocytes, and multinucle-ated giant cells, often with central caseous necrosis. In a person with tuberculosis, one of these granulomas is called a tubercle. Special stains, such as the Ziehl-Neelsen or other acid-fast stains, are required to demonstrate the mycobacteria. Because of the relative scarcity of the organisms within tissue, the special stains successfully demonstrate the organism in only 27% to 60% of cases. Therefore, a negative result does not rule out completely the possibility of tuberculosis.

Diagnosis

About 2 to 4 weeks after initial exposure, a cell-mediated hypersensitivity reaction to tubercular antigens develops. This reaction is the basis for the tuberculin (Mantoux or PPD) skin test. Positivity runs as high as 80% in developing nations; only 5% to 10% of the population in the United States is positive. A positive tuberculin skin test indicates exposure to the organism and does not distinguish infection from active disease. A negative tuberculin skin test does not rule out totally the possibility of tuberculosis. False-negative reactions have been documented in very elderly and immunocompromised patients and when the antigen was placed intradermally. The false-negative rate may be as high as 66% in patients with AIDS.

The diagnosis of active disease must be confirmed by special mycobacteria] stains and culture of infected sputum or tissue. Even if detected with special stains, identification of the organism by culture is appropriate. This identification is important because some forms of nontuberculous mycobacteria have a high level of resistance to traditional antituberculous therapy and frequently requires surgical excision. Because 4 to 6 weeks may be required to identify the organism in culture, anti-tuberculous therapy often is initiated before definitive classification. In the future, polymerase chain reaction (PCR) to identify *M. tuberculosis* DNA may accelerate the diagnosis without the need to wait on culture results.

Treatment and Prognosis

M. tuberculosis can mutate and develop resistance to single-agent medications. To combat this ability, multiagent therapy is the treatment of choice. Two multiagent protocols are recommended as first-line therapy against drug-susceptible tuberculosis. The choice is between (1) isoniazid (INH) plus rifampin for 9 months or (2) INH, rifampin, and pyrazinamide for 2 months, followed by INH and rifampin for 4 months. Other first-line medications include ethambutol and

streptomycin. Relapse rates of approximately 1.5% are seen. With an alteration of doses and the administration schedule, the response to therapy in patients with AIDS has been good, but relapses and progression of infection have been seen.

LEPROSY (HANSEN'S DISEASE)

Leprosy is a chronic infectious disease produced by *Mycabactenum leprae.* Because of worldwide efforts coordinated by the World Health Organization, a dramatic decrease in the prevalence of leprosy has been seen over the past 15 years. Since the mid-1980s, the number of estimated cases of active leprosy has dropped from between 10 and 12 million to 1.15 million, with the number of officially registered cases falling 85%. However, leprosy remains a public health problem in many areas of the world; approximately 82% of all currently reported cases are noted in five countries: Brazil, India, Indonesia, Myanmar, and Nigeria.

The organism has a low infectivity, and exposure rarely results in clinical disease. Small endemic areas of infection are present in Louisiana and Texas, but most patients in the United States have been infected abroad. The organism is thought by many to require a cool host body temperature for survival. Although the exact route of transmission is not known, the high number of organisms in nasal secretions suggests that in some cases the initial site of infection may be the nasal or oropharyngeal mucosa. Although humans are considered the major host, other animals (e.g., armadillo, chimpanzee, mangabey monkey) are thought to be additional possible reservoirs of infection. The nine-banded armadillo is relatively unique because of its low body core temperature, and it is naturally susceptible to the infection. Infected armadillos have been discovered in Louisiana.

For decades, leprologists have believed the bacillus is highly temperature dependent and produces lesions primarily in cooler parts of the body, such as the skin, nasal cavity, and palate. This concept has been questioned because the organism may be seen in significant numbers at sites of core body temperature, such as the liver and spleen. Recently, one investigator mapped common sites of oral involvement and compared this pattern to a map of the local temperature. This comparison demonstrated that the oral lesions tend to occur more frequently in the areas of the mouth with a lower surface temperature. The temperature-dependent theory of leprosy infection remains an area of interest and controversy.

Historically, two main clinical presentations are noted, and these are related to the immune reaction to the organism. The first, called tuberculoid leprosy, develops in patients with a high immune reaction. Typically, the organisms are not found in skin biopsy specimens, skin tests to heat-killed organisms (lepromin) are positive, and the disease is usually localized. The second form, lepromatous leprosy, is seen in patients who demonstrate a reduced cell-mediated immune response. These patients exhibit numerous organisms in the tissue, do not respond to lepromin skin tests, and exhibit diffuse disease. Borderline and less common variations exist. Active disease progresses through stages of invasion, proliferation, ulceration, and resolution with fibrosis. The incubation period is prolonged, with an average of 2 to 5 years for the tuberculoid type and 8 to 12 years for the lepromatous variant.

Clinical Features

Currently, leprosy is classified into two separate categories, *paucibacillary* and *multibacillary*, with the distinction influencing the recommended form of therapy. Because laboratory services such as skin smears often are not available, patients are increasingly being classified on clinical grounds using the number of lesions (primarily skin) and the number of body areas affected.

Paucibacillary leprosy corresponds closely to the tuberculoid pattern of leprosy and exhibits a small number of well-circumscribed, hypopigmented skin lesions. Nerve involvement usually results in anesthesia of the affected skin, often accompanied by a loss of sweating. Oral lesions are rare in this variant.

Multibacillary leprosy corresponds well to the lepromatous pattern of leprosy and begins slowly with numerous, ill-defined, hypopigmented macules or papules on the skin that, with time, become thickened. The face is a common site of involvement, and the skin enlargements can lead to a distorted facial appearance ***(leonine facies).*** Hair, including the eyebrows and lashes, often is lost.

Nerve involvement leads to a loss of sweating and decreased light touch, pain, and temperature sensors. This sensory loss begins in the extremities and spreads to most of the body. Nasal involvement results in nosebleeds, stuffiness, and a loss of the sense of smell. The hard tissue of the floor, septum, and bridge of the nose may be affected. Collapse of the bridge of the nose is considered pathognomonic.

Oral lesions are not rare in multibacillary leprosy, and reports on their prevalence vary from 19% to 60%. In an excellent review by Prabhu and Daftary of 700 patients with leprosy, the prevalence of facial skin involvement was 28%, and oral lesions were noted in 11.5%. The lesions tended to be more frequent during the first 5 years of the disease.

The sites that are cooled by the passage of air appear to be affected most frequently. The locations affected in order of frequency are the hard palate, soft palate, labial maxillary gingiva, tongue, lips, buccal maxillary gingiva, labial mandibular gingiva, and buccal mucosa. Effected soft tissue initially appears as yellowish to red, sessile, firm, enlarging papules that develop ulceration and necrosis, followed by attempted healing by secondary intention. Continuous infection of an area can lead to significant scarring and loss of tissue. Complete loss of the uvula and fixation of the soft palate may occur. The lingual lesions appear primarily in the anterior third and often begin as areas of erosion, which may develop into large nodules. Infection of the lip can result in significant macrocheilia.

Direct infiltration of the inflammatory process associated with lepromatous leprosy can destroy the bone underlying the areas of soft tissue involvement. Often the infection creates a unique pattern of facial destruction that has been termed facies leprosa and demonstrates a triad of lesions consisting of atrophy of the anterior nasal spine, atrophy of the anterior maxillary alveolar ridge, and endonasal inflammatory changes. Involvement of the anterior maxilla can result in significant bone erosion, with loss of the teeth in this area. Maxillary involvement in children can affect the developing teeth and produce enamel hypoplasia and short tapering roots. Dental pulp infection can lead to internal resorption or pulpal necrosis. Teeth with pulpal involvement may demonstrate a clinically obvious red discoloration of the crown. The cause of the discoloration is unknown but appears to be related to intrapulpal vascular damage secondary to the infection. Granulomatous involvement of the nasal cavity can erode through the palatal tissues and result in perforation.

The facial and trigeminal nerves can be involved with the infectious process. Facial paralysis may be unilateral or bilateral. Sensory deficits may affect any branch of the trigeminal nerve, but the maxillary division is the most commonly affected.

Histopathologic Features

Biopsy specimens of paucibacillary leprosy typically reveal the tuberculoid pattern that demonstrates granulomatous inflammation with well-formed clusters of epithelioid histiocytes, lymphocytes, and multinucleated giant cells. There is a paucity of organisms; when present, they can be demonstrated only when stained with acid-fast stains, such as the Fite method. Multibacillary leprosy is associated with lepromatous pattern that demonstrates no well-formed granulomas; the typical finding is sheets of lymphocytes intermixed with vacuolated histiocytes known as lepra cells. Unlike tuberculoid leprosy, an abundance of organisms can be demonstrated with acid-fast stains in the lepromatous variant.

Diagnosis

The definitive diagnosis is based on the clinical presentation and supported by the demonstration of acid-fast organisms on a smear or in the tissue. The organism cannot be cultivated on artificial media but *M. leprae* can be identified by using molecular biologic techniques. There is no reliable test to determine whether a person has been exposed to *M. leprae* without developing the disease; this creates difficulties in establishing the diagnosis and determining the prevalence of the infection.

Treatment and Prognosis

One of the major reasons for the decreasing prevalence of leprosy is the provision of an uninterrupted supply of free, high-quality medications in calendar blister packs to all patients regardless of the living conditions or remoteness of the location. Paucibacillary leprosy is treated

with a 6-month regimen of rifampin and dapsone, whereas patients with multibacillary leprosy receive 24 months of rifampin, dapsone, and clofazimine. Long-term follow up is recommended because of occasional relapses. Patients allergic to rifampin are treated with a 24-month course of clofazimine, ofloxacin, and minocycline.

After resolution of the infection, the therapy must be directed toward reconstruction of the damage, in addition to physiotherapy and education of the patients who must live not only with their physical damage but also with the psychologic stigmata. As medical therapy becomes more successful, the number of long-term survivors of the infection increases. Worldwide, it is estimated there are currently about 3 million individuals with leprosy-related impairments and disability.

HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

During the last two decades, more articles have been written on human immunodeficiency virus (HIV) and its related disease states than any other infectious process. A complete bibliography alone would be easily thicker than this chapter. Entire texts dedicated to HIV infection and acquired immunodeficiency syndrome (AIDS) are available and should be consulted for more detailed information.

AIDS came into the limelight in 1981. By 1992, 8 million people worldwide were thought to have been infected by HIV, with more than 5 million progressing to AIDS. Estimations at that time suggested the United States had between 1 and 1.5 million inhabitants infected with HIV. From the beginning of the epidemic to the dawn of the new century, 733,374 cases of AIDS have been reported in the United States to the Centers for Disease Control; of these individuals, 430,441 are dead. At the time of publication of the first edition of this text, the infection was thought to be nearly 100% fatal. Through treatment advances, the annual incidence of AIDS and related deaths have been dropping since 1996. This therapy is changing the face of HIV infection, with affected individuals demonstrating extended survival (resulting in an increased percentage of the population living with the virus).

In infected individuals, the virus can be found in most bodily fluids. HIV has been recovered from serum, blood, saliva, semen, tears, urine, breast milk, ear secretions, and vaginal secretions. The most frequent routes of transmission are sexual contact, parenteral exposure to blood, or transmission from mother to fetus during the perinatal period. Infection also has been documented to be caused by artificial insemination, breast-feeding from infected mothers, and organ transplantation. Although heterosexual transmission is increasing, most of the adults infected in the United States have been homosexual or bisexual men, intravenous drug abusers, hemophiliac patients receiving factor VIII before 1985, recipients of blood products, or heterosexual contacts with one of the other high-risk groups.

Researchers have debated the infectiousness of oral fluids. HIV has been found to be present in oral fluids, but saliva appears to reduce the ability of HIV to infect its target cells, lymphocytes. Reports of transmission by oral fluids are rare, and it appears this is not a significant source for the transmission of AIDS. In spite of this, anecdotal reports have documented the transmission of AIDS during breast-feeding from the oral fluids of postpartum infected infants to their previously noninfected mothers. In addition, rare examples have been documented reporting the transmission of HIV infection by contamination of the oral fluids during cunnilingus or repeated passionate kissing. Although rare, these anecdotal reports point out that oral fluids can be infectious and are not completely protective against oral introduction of HIV. In summary, the best safety against infection is avoidance of all body fluids of infected patients.

Initially, in the United States, AIDS was thought to be a disease that primarily affected whites and male homosexuals. Although men having sex with men remains the largest single risk factor, the nature of the epidemic is shifting. When compared with the cumulative data, more recent reports demonstrate a growing proportion of patients with AIDS occurring in blacks and Hispanics. Since 1996, blacks have out-numbered whites in new AIDS diagnoses and HIV-related deaths. Although the raw numbers are worrisome, the annual rates per 100,000 population dramatically highlight the ethnic shift. The proportion of women also is increasing steadily (23% in 1999), with a greater percentage infected heterosexually rather than through intravenous drug use.

The primary target cell of HIV is the CD4 + helper T lymphocyte. The DNA of HIV is incorporated into the DNA of the lymphocyte and, thus, is present for the life of the cell. In most viral infections, host antibodies that are protective against the organism usually are formed. In people with HIV infection,

antibodies are developed but are not protective. The virus may remain silent, cause cell death, or produce syncytial fusion of the cells, which disrupts their normal function. A subsequent decrease in T-helper cell numbers occurs, with a resultant loss in immune function. The normal response to viruses, fungi, and encapsulated bacteria is diminished.

On introduction of the HIV, an indefinite percentage of those infected will have an acute self-limited viral syndrome. This is followed by an asymptomatic stage, which averages 8 to 10 years. The length of the asymptomatic period is variable and may be affected by the nature of the virus, the host immune reaction, or external factors that may delay or accelerate the process. Almost inevitably, the final symptomatic stage develops.

Clinical Features

HIV infection initially may be asymptomatic or an acute response may be seen. The acute viral syndrome that occurs typically develops within 1 to 6 weeks after exposure in 50% to 70% of infected patients. The symptoms bear some resemblance to those of infectious mononucleosis (e.g., generalized lymphadenopathy, sore throat, fever, maculopapular rash, headache, myalgia, arthralgia, diarrhea, photophobia, peripheral neuropathies). Oral changes may include mucosal erythema and focal ulcerations.

The acute viral syndrome clears within a few weeks; during this period, HIV infection usually is not considered or investigated. A variable asymptomatic period follows. Some patients have persistent generalized lymphadenopathy, which may later resolve. In some patients (before development of overt AIDS), there is a period of chronic fever, weight loss, diarrhea, oral candidiasis, herpes zoster, and/or oral hairy leukoplakia. This has been termed *AIDS-related complex (ARC).*

The presentation of symptomatic, overt AIDS is highly variable and often is affected by a person's prior exposure to a number of chronic infections. The signs and symptoms described under ARC are often present, along with an increasing number of opportunistic infections or neoplastic processes. In 50% of the cases, pneumonia caused by the protozoan *Pneumocystis carinii* is the presenting feature leading to the diagnosis. Other infections of diagnostic significance include disseminated cytomegalovirus (CMV) infection, severe herpes simplex virus (HSV) infection, atypical mycobacterial infection, cryptococcal meningitis, and central nervous system (CNS) toxoplasmosis. Persistent diarrhea is commonplace and may be bacterial or protozoal in origin. Clinically significant neurologic dysfunction is present in 30% to 50% of patients, and the most common manifestation is a progressive encephalopathy known as *AIDS-dementia complex*.

Certain neoplastic processes also are associated with AIDS. Clinical descriptions of these cancers are presented in the portion of this text dealing with the oral manifestations of HIV infection. A vascular malignancy, Kaposi's sarcoma (KS), which otherwise is rare in the United States, has been reported in about 15% to 20% of patients with AIDS. This cancer appears associated with a sexually transmitted agent other than HIV: human herpesvirus type 8. AIDS-associated KS occurs primarily in homosexuals, but KS has been reported in homosexuals without HIV infection. This should remind clinicians that homosexuals with KS should not be labeled; "HIV-infected" until there is serologic proof. The prevalence of KS in HIV-infected patients has been decreasing and may be the result of the use of condoms, which may be preventing the transmission of herpesvirus 8.

Non-Hodgkin's lymphoma is the second most common malignancy. It is frequently found in extranodal sites, especially the CNS. Other cancers, including oral squamous cell carcinoma, have been documented in patients infected with HIV, but the association between AIDS and these cancers is not as strong.

A list of oral manifestations of AIDS is presented in Table 1. This list of common oral manifestations may change because of the impact of modern therapy on the disease. Current antiretroviral therapy has produced a significant decrease in the prevalence of HIV-related oral manifestations, with an altered ranking of the most commonly encountered pathoses. In one study, therapy appeared to decrease the frequency of oral candidiasis, hairy leukoplakia, destructive periodontal diseases, and KS; however, it increased the prevalence of HIV-associated salivary gland disease and human papillomavirus (HPV)-associated mucosal alterations.

Persistent generalized lymphadenopathy. After seroconversion, HIV disease often remains silent except for persistent generalized lymphadenopathy (PGL). The prevalence of this early clinical sign varies; however, in several studies it approaches 70%. PGL consists of lymphadenopathy that has been present for longer than 3 months and involves two or more extrainguinal sites. The most frequently involved sites are the posterior and anterior cervical, submandibular, occipital, and axillary nodes. Nodal enlargement fluctuates, usually is larger than 1 cm, and varies from 0.5 to 5.0 cm.

Because lymphoma is known to occur in this population, a lymph node biopsy may be indicated for localized or bulky adenopathy, when cytopenia or an elevated erythrocyte sedimentation rate is present, or when requested for patient reassurance. Histopathologic examination reveals florid follicular hyperplasia. Although not as predictive as oral candidiasis or hairy leukoplakia, PGL does warn of progression to AIDS; almost one third of affected and untreated patients will have diagnostic features of AIDS within 5 years.

Candidiasis. Oral candidiasis is the most common intraoral manifestation of HIV infection and often is the presenting sign that leads to the initial diagnosis. Its presence in a patient infected with HIV is not diagnostic of AIDS but appears to be predictive for the subsequent development of full-blown AIDS in untreated patients within 2 years. Prevalence studies vary widely, but approximately one third of HIV-infected individuals and more than 90% of patients with AIDS develop oral candidiasis at some time during their disease course. The following four clinical patterns are seen:

- Pseudomembranous
- Erythematous
- Hyperplastic
- Angular cheilitis

The first two variants constitute most of the cases. Although infrequently seen in immunocompetent patients, chronic multifocal oral involvement is common in patients who are infected with HIV.

The diagnosis of candidiasis often is obvious from the clinical presentation but can be confirmed by cytologic smear or biopsy. Biopsy specimens of involved mucosa demonstrate the candidal organisms embedded in the superficial keratin, but the typical inflammatory reaction often is deficient.

Treatment is much more difficult in patients with AIDS. Nystatin often is ineffective. Topical clotrimazole is associated with an improved response and typically produces a clinical cure rate that equals that of the systemic azoles. In spite of this success, topical therapy is associated with j a high recurrence rate. The systemic azoles (i.e., fluconazole, ketoconazole, itraconazole) produce longer disease-free intervals but are associated with another set of problems. Itraconazole and ketoconazole require gastric acidity for adequate absorption, and all three agents are associated with a number of drug interactions. In addition, widespread use of systemic azoles has led to an increased prevalence of drug-resistant candidiasis.

In patients who are receiving effective antiretroviral therapy and have a CD4 + count exceeding 50 cells/mm^3 plus no signs of esophageal involvement, topical clotri-mazole is the treatment of choice. Systemic therapy is recommended for patients not receiving effective antiretroviral therapy or for those with either esophageal involvement, a CD4 + count below 50, or a high viral load. Itraconazole in an oral solution has been shown to be particularly effective in a swish-and-swallow method.

Patients failing systemic azole therapy are candidates for intravenous amphotericin B if the patient's health supports its use. Topical amphotericin B is available, but little research exists on its relative effectiveness. Prophylactic antifungal therapy is not recommended unless frequent and severe recurrences are present.

HIV-associated periodontal disease. Three patterns of periodontal disease are associated strongly with HIV

ection:

- Linear gingival erythema
- Necrotizing ulcerative gingivitis
- Necrotizing ulcerative periodontitis

Linear gingival erythema initially was termed *HIV-related gingivitis* but ultimately was noted in association with other disease processes. This unusual pattern of gingivitis appears with a distinctive linear band of erythema that involves the free gingival margin and extends 2 to 3 mm apically. In addition,

the alveolar mucosa and gingiva may demonstrate punctate or diffuse erythema in a significant percentage of the cases. This form of gingivitis typically does not respond to improved plaque control and often exhibits a greater degree of erythema than would be expected for the amount of plaque in the area. Although some investigators believe linear gingival erythema occurs from an abnormal host immune response to subgingival bacteria, most believe this pattern of gingivitis represents an unusual pattern of candidiasis. In many instances, linear gingival erythema resolves after professional plaque removal, improved oral hygiene, and use of chlorhexidine rinses. Cases resistant to initial therapy typically respond to systemic antifungal medications such as fluconazole or ketoconazole.

Necrotizing ulcerative gingivitis (NUG) refers to ulceration and necrosis of one or more interdental papillae with no loss of periodontal attachment. Patients with NUG have interproximal gingival necrosis, bleeding, pain, and halitosis.

Necrotizing ulcerative periodontis (NUP) was previously termed *HIV-associated periodontitis;* however, it has not been deemed to be specific for HIV infection. NUP is characterized by gingival ulceration and necrosis associated with rapidly progressing loss of periodontal attachment. Although severe cases can affect all teeth, multiple isolated defects often are seen and contrast with the diffuse pattern associated with typical chronic periodontitis. Edema, severe pain, and spontaneous hemorrhage are common and often lead affected patients to seek care. Deep pocketing usually is not seen because extensive gingival necrosis typically coincides with loss of the adjacent alveolar bone. Loss of more than 6 mm of attachment within a 6-month period is not unusual. HIV-associated periodontitis does not respond to conventional periodontal therapy.

The treatment of NUG and NUP revolves around debridement, antimicrobial therapy, immediate follow-up care, and long-term maintenance. The initial removal of necrotic tissue is necessary, combined with povidoneiodine irrigation. The use of systemic antibiotics usually is not necessary, but metronidazole has been administered to patients with extensive involvement that is associated with severe acute pain. All patients should use chlorhexidine mouth rinses initially and for long-term
maintenance. After initial debridement, follow-up removal of additional diseased tissue should be performed within 24 hours and again every 7 to 10 days for two to three appointments, depending on the patient's response. At this point, monthly recalls are necessary until the process stabilizes; evaluations then are performed every 3 months.

In patients with gingival necrosis, the process occasionally extends away from the alveolar ridges and creates massive areas of tissue destruction termed necrotizing stomatitis. The process clinically resembles noma and may involve predominantly soft tissue or extend into the underlying bone, resulting in extensive sequestration. Although this process initially was thought to be an extension of NUP, necrotizing stomatitis has arisen on the oral mucosa separate from the gingiva (not overlying bone).

In the absence of gingival involvement, the clinical features of necrotizing stomatitis are nonspecific and mandate biopsy. In many instances, the areas of soft tissue ulceration and necrosis demonstrate infection with one of more agents, such as herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). On occasion, evaluations for HSV, CMV, and EBV are negative, leading one group to suggest that some lesions may represent an unusual immune reaction to the HIV. Upon biopsy, these ulceronecrotic lesions often demonstrate leukocytoclasia, histiocytic vasculitis, and an inflammatory infiltrate with numerous large atypical histiocytes.

Herpes simplex virus (HSV). Recurrent HSV infections occur in about the same percentage of HIV-infected patients as they do in the immunocompetent population (10% to 15%); however, the lesions are more widespread, occur in an atypical pattern, and may persist for months. The prevalence of HSV lesions increases significantly once the CD4 + count drops below 50. Herpes labialis may extend to the facial skin and exhibit extensive lateral spread. Persistence of active sites of HSV infection for more than 1 month in a patient infected with HIV is one accepted definition of AIDS. The clinical presentations of recurrences in immunocompro-mised patients and appropriate therapy and maintenance have been discussed in the text on herpesvirus.

As mentioned in the discussion of necrotizing stomatitis, evaluation for HSV should be performed in all persistent oral ulcerations in HIV-infected individuals. In these ulcerations, investigators have discovered HSV in 10% to 19% (with an additional 10% to 28% exhibiting co-infection by HSV and CMV).

Varicella-zoster virus (VZV). Recurrent VZV infection j (herpes zoster) is fairly common in HIV-infected patients, but the course is more severe, with increased morbidity and mortality rates. Many of these patients are younger than age 40, in contrast to cases in immunocompetent patients that usually arise later in life. In the early stages of HIV-related immunosuppression, herpes zoster usually is confined to a dermatome but persists longer than usual. In full-blown AIDS, herpes zoster usually begins in a classic dermatomal distribution; however, subsequent cutaneous dissemination is not unusual. When present intraorally, the involvement often is severe and occasionally leads to bone sequestration and loss of teeth. Associated pain typically is intense. Although per-oral antiviral medications are beneficial in immunocompetent patients, intravenous acyclovir is recommended for severe herpes zoster in the absence of an intact immune system.

Epstein-Barr virus (EBV). Although EBV is thought to be associated with several forms of lymphoma in HIV-Infected patients, the most common EBV-related lesion in patients with AIDS is oral hairy leukoplakia (DHL). This lesion has a somewhat distinctive (but not diagnostic) pattern of hyperkeratosis and epithelial hyperplasia that is characterized by white mucosal lesions that do not rub off.

Most cases of OHL occur on the lateral border of the tongue and range in appearance from faint white vertical streaks to thickened and furrowed areas of leukoplakia, exhibiting a shaggy keratotic surface. The lesions may become extensive and cover the entire dorsal and lateral surfaces of the tongue. Rarely, involvement also has been observed on the buccal mucosa, soft palate, pharynx, or esophagus.

Histopathologically, OHL exhibits thickened parakeratin, which demonstrates surface corrugations or thin projections. The epithelium is hyperplastic and contains a patchy band of lightly stained "balloon cells" in the upper spinous layer. Close examination of the superficial epithelium reveals scattered cells with nuclear clearing and a characteristic pattern of peripheral margination of chromatin termed *nuclear beading*. The nuclear alterations are created by extensive EBV replication that displaces the chromatin to the nuclear margin. Dysplasia is not noted. Heavy candidal infestation of the parakeratin layer is typical, and the normal inflammatory reaction to the fungus usually is absent.

In the routine management of HIV-infected patients, the clinical features typically are sufficient for a presumptive diagnosis. When definitive diagnosis is necessary, demonstration of EBV within the lesion is required and can be achieved by *in situ* hybridization, PCR, immunohistochemistry, Southern blotting, or electron microscopy.

Treatment of OHL usually is not needed, although slight discomfort or aesthetic concerns may necessitate therapy. Acyclovir or desiclovir produces rapid resolution, but recurrence is expected with a discontinuation of therapy. Topical treatment with retinoids or podophyllum resin has resulted in temporary remissions. In addition, HIV therapy with zidovudine appears to affect EBV and result in significant regression.

Although rare instances of OHL have been reported in immunocompetent individuals, most cases arise in immunocompromised persons. OHL also has been reported in heart, kidney, liver, and bone marrow transplant recipients, but its presence in the absence of a known cause of immunosuppression strongly suggests HIV infection. Discovery of OHL in "normal" patients mandates a thorough physical evaluation to rule out immunocompromised status. The presence of OHL in HIV-infected patients is a signal of severe immune suppression and more advanced disease.

Kaposi's sarcoma (KS). KS is a multifocal neoplasm of vascular endothelial cell origin. Before AIDS, KS was rare in North America and was found classically in patients over the age of 60. Since the beginning of the HIV epidemic, however, most cases have been seen in association with AIDS. Human herpesvirus type 8 (HHV-8) is noted within the tumor and thought to be involved in the neoplasm's development.

KS begins with single or, more frequently, multiple lesions of the skin or oral mucosa. The trunk, arms, head, and neck are the most commonly involved anatomic sites. Oral lesions are seen in approximately 50% of affected patients and are the initial site of involvement in 20% to 25%. Although any mucosal site maybe involved, the hard palate, gingiva, and tongue are affected most frequently. When present on the palate or gingiva, the neoplasm can invade bone and create tooth mobility. The lesions begin as flat, brown or reddish purple zones of discoloration that do not blanch with pressure. With time, the involved areas may develop into plaques or nodules. Pain, bleeding, and necrosis may become a problem and necessitate therapy.

A biopsy is required to make the definitive diagnosis, although a presumptive diagnosis is sometimes made from the clinical presentation and history. It must be remembered that similar clinical lesions can occur in HIV-infected patients who exhibit bacillary angiomatosis, the multifocal vascular proliferation associated with the cat-scratch bacillus.

KS is a progressive malignancy that may disseminate widely to lymph nodes and various organ systems. Extensive systemic therapy often further depresses the immune system, thereby increasing the susceptibility of the patient to infection and other cancers. Achievement permanent cure has been elusive, although most patients with AIDS-related KS die of other complications, such as opportunistic infections. Therefore, treatment objectives usually are palliative. KS responds to radiation or systemic chemotherapy (singly or in combination), such as vinblastine, vincristine, etoposide, bleomycin, Adriamycin, actinomycin D, doxorubicin, or la-interferon.

Oral lesions frequently are a cause of major morbidity, as a result of pain, bleeding, and functional interferences. Intralesional injection of oral lesions with vinblastine is effective and may be repeated if required. Intralesional injection of a sclerosing agent, sodium tetradecyl sulfate, has been effective for problematic intraoral lesions less than 2.5 cm in diameter. Problematic lesions also may be removed by surgical excision, cryotherapy, laser ablation, or electrosurgery. Concerns exist about the use of the latter two methods because of aerosolization of viral particles that may place the surgical team at risk.

Significant regression of KS has been noted in a number of patients receiving antiretroviral therapy such as indinavir, ritonavir, or saquinavir. It is not known if this response is due to an improvement in the immune system of the host or a direct antiviral effect against HHV-8.

Less common oral and maxillofacial manifestations of HIV infection

Aphthous ulcerations. Lesions that are similar clinically to aphthous ulcerations occur with increased frequency in patients infected with HIV. All three forms (minor, major, and herpetiform) are seen; surprisingly, however, almost two thirds of the patients have the usually uncommon herpetiform and major variants. As immunosuppression becomes more profound, major aphthous ulcerations demonstrate an increased prevalence.

Treatment with potent topical or intralesional corticosteroids has been successful in a number of patients. Not all lesions respond, and recurrences are common. Secondary candidiasis may be a complication of therapy. Systemic corticosteroids also may prove beneficial but typically are avoided in an attempt to prevent further immune depression. For lesions nonresponsive to topical steroids, thalidomide has been found to be advantageous in many patients. Thalidomide must be used cautiously for only a short term because of its ability to enhance the production of HIV. In a limited number of patients, granulocyte colony stimulating factor has produced rapid and sustained resolution of aphthous ulcerations that were resistant to therapy with topical corticosteroids, cyclosporine, and thalidomide.

Biopsy of any chronic mucosal ulceration clinically diagnosed as an aphthous ulceration should be considered if the lesion is atypical clinically or does not respond to therapy. In such cases, biopsy often reveals another cause, such as HSV, CMV, deep fungal infection, or neoplasia.

Human papillomavirus (HPV). HPV is responsible for several facial and oral lesions in immunocompetent patients, the most frequent of which are the *verruca vulgaris (common wart)* and oral *squamous papilloma*. An increased prevalence of HPV-related lesions is noted in HIV-infected patients, and most are located in the anogenital areas. Oral involvement also may be seen. Although usual types of HPV may be present in intraoral lesions, HIV-infected patients often demonstrate more unusual variants such as HPV-7 (associated with butcher's warts) or HPV-32 (often noted in Heck's disease).

The oral lesions usually are multiple and may be located on any mucosal surface. The labial mucosa, tongue, buccal mucosa, and gingiva are frequent sites. The lesions may exhibit a cluster of white, spikelike projections, pink cauliflower-like growths, or slightly elevated sessile papules.

Histopathologically, the lesions may be sessile or papillary and covered by acanthotic or even hyperplastic stratified squamous epithelium. The affected epithelium often demonstrates vacuolization of numerous epithelial cells (i.e., koilocytosis) and occasionally may exhibit mild variation in nuclear size. Immunohistochemistry or DNA in situ hybridization often is used to confirm the presence and type of HPV within histopathologic specimens.

Dysplasia has been noted within HPV-related lesions in patients with AIDS and mandates close observation of affected patients for development of squamous cell carcinoma. The treatment of choice is surgical removal; however, recurrences are common, especially in patients with significant immune deficiency. Other therapeutic modalities that have been used include topical podophyllin, interferon, cryosurgery, laser ablation, and electrocoagulation. If one of the latter two choices is used, the surgical team must be wary of the resultant plume that may contain infectious HPV.

Histoplasmosis. Histoplasmosis, the most common p endemic respiratory fungal infection in the United States, is produced by *Histoplasma capsulation*. In healthy patients, the infection typically is subclinical and self-limiting, but clinically evident infections do occur in pimmunocompromised individuals. Although a number of deep fungal infections are possible in patients with AIDS, histoplasmosis is the most common, with disseminated disease noted in approximately 5% of AIDS patients residing in areas where the fungus is endemic. In patients 1 with AIDS, diagnosis of histoplasmosis also has been I documented in nonendemic areas, possibly from reactivation of a previous subclinical infection.

The signs and symptoms associated with dissemination are nonspecific and include fever, weight loss, splenomegaly, and pulmonary infiltrates. Oral lesions are not uncommon and usually are caused by blood-borne organisms or spread from pulmonary involvement. On occasion, the initial diagnosis is made from the oral changes, with some patients demonstrating involvement Isolated to the oral cavity. Although intrabony infection in the jaws has been reported, the most common oral presentation of histoplasmosis is a chronic, indurated mucosal ulceration with a raised border. The oral lesions may be singular or multiple, and any area of the oral mucosa may be involved.

Microscopically, the small fungal organisms are visible within the cytoplasm of histiocytes and multinucleated giant cells. These phagocytic cells may be present in sheets or in organized granulomas. The therapy of choice for disseminated histoplasmosis has been intravenous amphotericin B, but itraconazole has been shown to be effective with fewer adverse reactions and better patient compliance. Ketoconazole is another alternative, but its hepatotoxicity makes this approach a less desirable form of therapy.

Molluscum contagiosum. Molluscum contagiosum is an infection of the skin caused by *a* poxvirus. The lesions are small, waxy, dome-shaped papules that often demonstrate a central depressed crater. In immunocompetent individuals, the lesions are self-limiting and typically involve the genital region or trunk. In patients with AIDS, hundreds of lesions may be present, with many exhibiting little tendency to undergo spontaneous resolution, and some occasionally obtaining large size. Approximately 5% to 10% of HIV-infected patients are affected, and the facial skin commonly is involved.

Histopathologically, the surface epithelium forms several hyperplastic downgrowths. This involuting epithelium contains numerous large, intracytoplasmic inclusions known as *molluscum bodies*. In the center of the lesion, the keratin layer often disintegrates and releases the adjacent molluscum bodies, hence the central crater.

Local therapy (e.g., curettage, cryosurgery, cautery) usually is painful and often disappointing because of frequent recurrences. Several separate reports have documented resolution of widespread and recalcitrant lesion after successful initiation of highly active antiretroviral therapy. It is not known if these responses are secondary to immune reconstitution or the antiviral effects of the therapy.

Thrombocytopenia. Thrombocytopenia has been reported in nearly 10% of patients with HIV infection and may occur at any time during the course of the disease. Some reports show that megakaryocytes have CD4 molecules and may be an additional target for the HIV virus. Cutaneous lesions are present in most cases, but oral lesions do occur with petechiae, ecchymosis, or spontaneous gingival hemorrhage.

HIV-associated salivary gland disease. HIV-associated salivary gland disease also can arise anytime during infection. Clinically obvious salivary gland disease is noted in approximately 5 % of HIV-infected patients, with a greater prevalence noted in children. The main clinical sign is salivary gland enlargement, particularly affecting the parotid. Bilateral involvement is seen in about 60% of the patients with glandular changes and often is associated with cervical lymphadenopathy.

As a result of a genetically influenced alteration of the immune response to HIV infection, some patients develop *diffuse infiltrative lymphocytosis syndrome* (DILS), which is associated with a more favorable prognosis of their HIV infection. Affected individuals reveal CDS lymphocytosis and lymphadenopathy along with salivary gland enlargement. Although the parotid is affected most

commonly, minor gland involvement is possible. The glandular involvement arises from CD8-lymphocytic infiltration and often is followed by lymphoepithelial cyst formation in the parotid.

The most widely accepted therapy for DILS is oral prednisone or antiretroviral therapy, although some patients have been treated with parotidectomy or radiation therapy. Affected patients exhibit an increased risk for B-cell lymphoma; observation with histopathologic monitoring by fine-needle aspiration is prudent. Associated xerostomia is variable and treated in a manner similar to that of cases associated with non-HIV disease (i.e., maintenance of good oral health and the use of sialo-gogues and saliva substitutes).

Hyperpigmentation. Hyperpigmentation of the skin, nails, and mucosa has been reported in HIV-infected patients. The changes are similar microscopically to focal melanosis, with increased melanin pigmentation observed in the basal cell layer of the affected epithelium. Several medications taken by AIDS patients (e.g., ketoconazole, clofazimine, pyrimethamine, zidovudine) may cause the increased melanin pigmentation. Adrenocortical destruction has been reported from several of the infections associated with AIDS, resulting in an Addisonian pattern of pigmentation. Finally, pigmentation with no apparent cause has arisen in HIV-infected patients, and some investigators have theorized that this may be a direct result of the HIV infection.

Lymphoma. Lymphoma is the second most common malignancy in HIV-infected individuals. This neoplasm occurs in approximately 3% of those with the virus, a prevalence 60 times greater than the normal population. Most are non-Hodgkin's B-cell lymphomas, but reports of T-cell and Hodgkin's lymphomas exist. A relationship between EBV and non-Hodgkin's lymphomas has been documented, and many investigators believe these tumors arise from a combination of EBV, antigenic stimulation, and immune dysfunction.

Lymphoma in patients with AIDS is typically exhibited in extranodal locations, with the CNS being the most common site. Oral lesions may occur and most often present as a soft tissue enlargement of the palate or gingiva. Intraosseous involvement also has been documented, and it may resemble diffuse progressive periodontitis with loss of periodontal attachment and loosening of teeth. In these cases, widening of the periodontal ligament and loss of lamina dura frequently are noted and represent clues to the diagnosis.

The treatment usually is combination chemotherapy, and radiation is reserved for local control of the disease. These malignancies are aggressive, and survival usually is measured in months from the date of discovery. Although highly active antiretroviral therapy has reduced dramatically the prevalence of opportunistic infections and Kaposi's sarcoma in HIV-infected patients, a major decrease in lymphoma has not been documented. It appears that non-Hodgkin's lymphoma will become increasingly more important as a cause of morbidity and mortality in patients infected with HIV.

Oral squamous cell carcinoma. Squamous cell carcinoma of the oral cavity, pharynx, and larynx has been reported in HIV-infected patients. These neoplasms are associated with the same cancer risk factors as the general population but tend to occur at a younger age. Similar clinical presentations and anatomic distribution of these carcinomas are noted. It appears HIV infection may accelerate the development of squamous cell carcinoma, possibly because of impaired immune surveillance.

Treatment of squamous cell carcinoma is not significantly different for HIV-infected patients and consists of surgical resection, radiation therapy, or combined radiation and chemotherapy. Clinical staging can be problematic because of HIV-related cervical lymphadenopathy. In these cases, cross-sectional CT or MRI can be performed in an attempt to distinguish lymph nodes enlarged by lymphoproliferative disease from those containing metastatic carcinoma. The majority of HIV-infected patients with squamous cell carcinoma are diagnosed with advanced disease and exhibit a less favorable prognosis.

Diagnosis

Confirmation of H1V infection can be made by viral culture or by detection of HIV antibodies or antigens. The standard screening tool is the enzyme immunoassay (EIA) for antibodies to HIV. This test can have false-positive results or cross-reactions; therefore, it should be repeated and followed by the more accurate Western blot antibody assay. Other alternatives include radioim-munoprecipitation (RIPA),

rapid latex agglutination assay, and dot-blot immunobinding assay. All of these evaluations are used to detect antibodies to HIV.

In an attempt to improve the safety of the blood supply, a few assays have been approved by the PDA to detect viral antigens before development of anti-HIV antibodies. These tests are not used widely and include the p24 antigen capture assay and polymerase chain reaction (PCR) for detection of HIV DNA that may be integrated into the host DNA. This latter method may be used to identify someone who was infected recently or HIV carriers who otherwise have negative antigen or antibody findings.

The diagnosis of AIDS is indicated if the patient has laboratory evidence of HIV infection combined with documentation of less than 200 CD4 + T lymphocytes per microliter or a CD4 + T-lymphocyte percentage of total lymphocytes of less than 14. In addition, the diagnosis of AIDS can be made in an HIV-infected person if one of the indicator diseases listed in Box 1 has been documented.

Box 1 *Indicator Diseases Used in the Diagnosis of Acquired Immunodeficiency Syndrome*

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis, esophageal
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis, extrapulmonary
6. Cryptosporidiosis, chronic intestinal (> 1 month's duration)
7. Cytomegalovirus disease (other than liver, spleen, or nodes)
8. Cytomegalovirus-induced retinitis (with loss of vision)
9. Encephabpathy, HIV-related
10. Herpes simplex: chronic ulcer or ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (>1 month's duration)
13. Kaposi's sarcoma
14. Lymphoma, Burkitt's (or equivalent term)
15. Lymphoma, immunoblastic (or equivalent term)
16. Lymphoma, primary, of brain
17. *Mycobacterium avium* complex or *M. kansasii,* disseminated or extrapulmonary
18. *Mycobacterium tuberculosis,* any site (pulmonary or extrapulmonary)
19. Mycobacterium, other species or unidentified species, disseminated, or extrapulmonary
20. *Pneumocystis carinii* pneumonia
21. Pneumonia, recurrent
22. Progressive multifocal feukoencephalopathy
23. *Salmonella* septicemia, recurrent
24. Toxoplasmosis of brain
25. Wasting syndrome as a result of AIDS

Treatment and Prognosis

As mentioned previously, HIV infection initially was considered fatal; however, the introduction of highly active antiretroviral therapy (HAART) has altered the course of the epidemic. The annual incidence of AIDS and related deaths in the United States dropped for the first time in 1996 and has continued to do so since that time. Three types of medications are available. Initial regimens consist of two nucleoside reverse transcriptase inhibitors and one or two protease inhibitors. Alternatively, two nucleoside reverse transcriptase inhibitors and a nonnucleoside reverse transcriptase inhibitor can be used.

The current therapeutic approaches have driven HIV to undetectable levels in many patients, with a resultant clinically significant reconstitution of the immune system. With the current antiretroviral medications, total HIV eradication would take at least a decade and presently is not a realistic goal. Although no cure exists, survival times are increasing as a result of earlier diagnosis and improved therapy.

Although antiretroviral therapy is effective for many patients, it is expensive. In addition, this treatment often is associated with significant adverse reactions, may not be effective in all patients, or may fail after a period of initial success. Work is proceeding toward the development of a safe and effective vaccine against HIV infection, but complex issues slow the progress. Advances in therapy and prevention of HIV infection occur daily; however, the best defense against the disease is prevention of the initial infection.

Box 7-2 *Antiretroviral Therapy*

1. Nucleoside reverse-transcriptase inhibitors
    - Abacavir, didanosine, lamivudine, stavudine, zalcitabine, or zidovudine
2. Nonnucleoside reverse transcriptase inhibitors
    - Detavirdine, efavirenz, or nevirapine
3. Protease inhibitors
    - Amprenavir, indinavir, nelfinavir, ritonavir, or saquinavir

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